

NOVEL 1,4-BENZOTHIAZEPINE AND 1,5-BENZOTHIAZEPINE COMPOUNDS
AS INHIBITORS OF APICAL SODIUM CO-DEPENDENT BILE ACID
TRANSPORT AND TAUROCHOLATE UPTAKE

- [01] This application claims priority to provisional U.S. Application Ser. No. 60/220,966 filed July 26, 2000, incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

- [02] The present invention relates to compounds, pharmaceutical compositions, and methods for the treatment of a hyperlipidemic condition in a subject. More particularly, the present invention relates to novel 1,4-benzothiazepine and 1,5-benzothiazepine compounds that are useful as apical sodium co-dependent bile acid transport inhibitors.

BACKGROUND OF THE INVENTION

- [03] The major metabolic fate of cholesterol in the human body is in the hepatic synthesis of bile acids. Bile acids are both passively and actively reabsorbed from the small intestine and recycled via the enterohepatic circulation to conserve the total pool of bile acids. Dietschy, "Mechanisms for the intestinal absorption of bile acids", J. Lipid Res., 9:297-309 (1968). Bile acids undergo passive absorption in the proximal small intestine and active transport in the terminal ileum. Love et al., "New insights into bile acid transport", Curr. Opin. Lipidol., 9(3):225-229 (1998). Ileal active transport accounts for the majority of intestinal bile acid uptake and is the exclusive route for taurine-conjugated bile acids. Id. Ileal active transport is mediated by the apical sodium co-dependent bile acid transporter ("ASBT", also known as the ileal bile acid transporter or "IBAT") localized to the distal one-third of the ileum. Craddock et al., "Expression and transport properties of the human ileal and renal sodium-dependent bile acid transporter", Am. J. Physiol., 274 (Gastrointest. Liver Physiol. 37):G157-G169 (1998).
- [04] An equilibrium generally exists between hepatic cholesterol and the bile acid pool. Interruption of the enterohepatic recirculation of bile acids (e.g., the

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binding of intestinal bile acids to a sequestering resin such as cholestyramine; the surgical removal of the ileum to physically eliminate ileal ASBT; or the specific inhibition of ileal ASBT) results in a decrease in the liver bile acid pool and stimulates increased hepatic synthesis of bile acids from cholesterol (i.e., an upregulation of cholesterol-7 α -hydroxylase activity), eventually depleting the liver's pool of esterified cholesterol. In order to maintain liver cholesterol levels necessary to support bile acid synthesis, the de novo synthesis of cholesterol increases in the hepatocytes (i.e., an upregulation of 3-hydroxy-3-methylglutaryl coenzyme-A reductase activity) and also increases the uptake of serum cholesterol by upregulating the number of cell surface low density lipoprotein cholesterol receptors ("LDL receptors"). The number of hepatic LDL receptors directly impacts serum low density lipoprotein ("LDL") cholesterol levels, with an increase in the number of LDL receptors resulting in a decrease in serum cholesterol. The net result, therefore, is that serum LDL cholesterol levels decrease when intestinal bile acid reabsorption is reduced. Stedronsky, in "Interaction of bile acids and cholesterol with nonsystemic agents having hypocholesterolemic properties," *Biochimica et Biophysica Acta*, 1210 (1994) 255-287 discusses biochemistry, physiology, and known active agents surrounding bile acids and cholesterol. Agents that inhibit the transport of bile acids across the tissue of the ileum, therefore, can cause a decrease in the levels of cholesterol in blood serum.

- [05] A large number of adults have cholesterol levels that exceed recommended levels and can be considered as having hypercholesterolemia. If left untreated, such hypercholesterolemia can result, for example, in atherosclerosis and complications of atherosclerosis such as myocardial infarction, stroke and peripheral vascular disease. Accordingly, the development of new therapeutic agents (such as ASBT inhibitors) that overcome the problems associated with, and/or show improved performance relative to, the therapeutic agents disclosed in the literature would be desirable. The present invention therefore comprises novel 1,4- and 1,5-benzothiazepines that represent an improvement over the therapeutic agents previously disclosed for use in the treatment of a

hyperlipidemic condition, together with pharmaceutical compositions and methods of use thereof.

- [06] Those 1,4- and 1,5-benzothiepinines that have been disclosed in the literature as agents for the treatment of a hyperlipidemic condition include the following:
- [07] WO93/16055 discloses selected 1,4-benzothiazepines as useful in the treatment of a hyperlipidemic condition.
- [08] WO94/18183 discloses selected 1,4-benzothiazepines as useful in the treatment of a hyperlipidemic condition.
- [09] WO94/18184 discloses selected 1,4-benzothiazepines as useful in the treatment of a hyperlipidemic condition.
- [10] WO96/05188 discloses selected 1,4-benzothiazepines as useful in the treatment of a hyperlipidemic condition.
- [11] WO98/05657 discloses selected 2,3-dihydro-1,4-benzothiazepines as therapeutic agents.
- [12] U.S. Patent 5,910,494 discloses selected 1,4-benzothiazepines as useful in the treatment of a hyperlipidemic condition.
- [13] U.S. Patent 6,020,330 discloses selected 1,4-benzothiazepines as useful in the treatment of a hyperlipidemic condition.
- [14] WO96/16051 discloses selected 1,5-benzothiazepines as useful in the treatment of a hyperlipidemic condition.
- [15] WO99/35135 discloses selected 1,5-benzothiazepines as useful in the treatment of a hyperlipidemic condition.
- [16] M. Booker et al., "Ileal Bile Acid Transport Inhibitors As Potential Hypocholesterolemic Agents," *Curr. Opin. In Cardiovascular, Pulmonary & Renal Invest. Drugs*, Vol. 2, No. 3, pp. 208-215 (2000), discloses 1,4- and 1,5-

benzothiepienes (including Glaxo Wellcome compounds 2164U90 and 264W94) as useful for the treatment of a hyperlipidemic condition.

- [17] In addition, selected benzothiepienes have been disclosed in the literature as agents for the treatment of a hyperlipidemic condition. For example, U.S. Patent 5,994,391 discloses substituted benzothiepine compounds (including 5-(substituted phenyl)-benzothiepine compounds) for use as ASBT inhibitors. WO99/64409 discloses similar 5-(substituted phenyl)-benzothiepine compounds wherein the phenyl substituent comprises a mono-, di-, tri- or tetrasaccharide moiety as useful for the treatment of a hyperlipidemic condition.
- [18] Further, other classes of compounds have been disclosed in the literature as agents for the treatment of a hyperlipidemic condition. For example, PCT Patent Application No. WO94/24087 discloses a group of substituted naphthalene compounds as useful for the treatment of a hyperlipidemic condition.

BRIEF SUMMARY OF THE INVENTION

- [19] A first aspect of the invention comprises novel 1,4- and 1,5-benzothiazepine compounds corresponding to Formula I (as later defined in the Detailed Description) that are effective agents for the treatment of a hyperlipidemic condition or conditions.
- [20] Another aspect of the invention comprises pharmaceutical compositions comprising one or more of the novel 1,4- and 1,5-benzothiazepine compounds corresponding to Formula I that are suitable for use in treating a hyperlipidemic condition or conditions.
- [21] Still another aspect of the invention comprises methods for the treatment of a hyperlipidemic condition or conditions comprising administering to a subject a therapeutically effective amount of one or more of the novel 1,4- and 1,5-benzothiazepine compounds corresponding to Formula I.

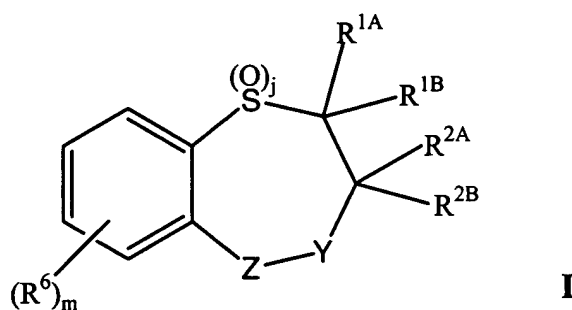
- [22] Still another aspect of the invention comprises methods of making the novel 1,4- and 1,5-benzothiazepine compounds corresponding to Formula I.
- [23] Still another aspect of the invention comprises novel 1,4- and 1,5-benzothiazepine compounds corresponding to Formula VII (as later defined in the Detailed Description) that are effective agents for the treatment of a hyperlipidemic condition or conditions.
- [24] Still another aspect of the invention comprises pharmaceutical compositions comprising one or more of the novel 1,4- and 1,5-benzothiazepine compounds corresponding to Formula VII that are suitable for use in treating a hyperlipidemic condition or conditions.
- [25] Still another aspect of the invention comprises methods for the treatment of a hyperlipidemic condition or conditions comprising administering to a subject a therapeutically effective amount of one or more of the novel 1,4- and 1,5-benzothiazepine compounds corresponding to Formula VII.
- [26] Still another aspect of the invention comprises methods of making the novel 1,4- and 1,5-benzothiazepine compounds corresponding to Formula VII.
- [27] Other aspects of the invention will be in part apparent and in part pointed out hereinafter.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS OF THE INVENTION

- [28] The present invention comprises novel 1,4- and 1,5-benzothiazepine compounds that are safe and effective anti-hyperlipidemic agents. These compounds generally exhibit one or more superior characteristics relative to conventional 1,4- and 1,5-benzothiazepine compounds previously disclosed in the literature as therapeutic agents. These characteristics can include, but are not limited to, for example: (a) improved potency, (b) an improved solubility profile, (c) improved compatibility with conventional routes of oral administration, (d) an improved safety profile, and (e) elimination of a chiral

center at the 3-position carbon ring atom without a significant loss in potency relative to the corresponding conventional 1,4- and 1,5-benzothiazepine compounds having a chiral center at the 3-position carbon ring atom and lacking the novel substituent(s) present in the claimed compounds.

- [29] The compounds of the present invention are useful for, but not limited to, the treatment of a hyperlipidemic condition or conditions in a subject, including the prophylactic or preventative treatment of a hyperlipidemic condition or conditions in a subject. The methods, combinations, compositions and kits of the present invention also are useful for the prophylaxis and/or treatment of gallstones. Besides being useful for human treatment, these methods and compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.
- [30] More specifically, the present invention comprises a class of compounds useful in treating a hyperlipidemic condition that is defined by Formula I:



- [31] wherein:
- [32] j is 0, 1 or 2; and
- [33] m is 0, 1, 2, 3 or 4; and
- [34] R^{1A} and R^{1B} are independently selected from the group consisting of hydrogen and hydrocarbyl, wherein said hydrocarbyl may be optionally substituted with one or more groups comprising one or more heteroatoms, and wherein said hydrocarbyl optionally may have one or more carbon atoms

replaced by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen, sulfur and phosphorus;

[35] R^{2A} and R^{2B} are independently selected from the group consisting of hydrogen and hydrocarbyl, wherein said hydrocarbyl may be optionally substituted with one or more groups comprising one or more heteroatoms, and wherein said hydrocarbyl optionally may have one or more carbon atoms replaced by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen, sulfur and phosphorus;

[36] one of Z and Y is NR^3 and the other of Z and Y is CHR^4 ;

[37] wherein R^3 and R^4 are independently selected from the group consisting of hydrogen, oxo, hydrocarbyl; $-R^5$; $-OR^9$; $-NR^9R^{10}$; $-SR^9$; $-S(O)R^9$; $-SO_2R^9$; and $-SO_3R^9$; wherein said hydrocarbyl may be optionally substituted with one or more groups comprising one or more heteroatoms, and wherein said hydrocarbyl optionally may have one or more carbon atoms replaced by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen, sulfur and phosphorus;

[38] wherein R^9 and R^{10} are independently selected from the group consisting of hydrogen; hydrocarbyl; amino; and hydrocarbylamino; wherein said hydrocarbyl moieties may be optionally substituted with one or more groups comprising one or more heteroatoms, and wherein said hydrocarbyl moieties optionally may have one or more carbon atoms replaced by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen, sulfur and phosphorus; and

[39] R^5 is selected from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; $-OR^9$; $-SR^9$; $-S(O)R^9$; $-SO_2R^9$; and $-SO_3R^9$;

- [40] wherein R^5 group optionally may be substituted with one or more radicals independently selected from the group consisting of halogen; $-NO_2$; $-CN$; oxo; hydrocarbyl; $-OR^{13}$; $-NR^{13}R^{14}$; $-SR^{13}$; $-S(O)R^{13}$; $-SO_2R^{13}$; $-SO_3R^{13}$; $-NR^{13}OR^{14}$; $-NR^{13}NR^{14}R^{15}$; $-CO_2R^{13}$; $-OM$; $-SO_2OM$; $-SO_2NR^{13}R^{14}$; $-C(O)NR^{13}R^{14}$; $-C(O)OM$; $-COR^{13}$; $-NR^{13}C(O)R^{14}$; $-NR^{13}C(O)NR^{14}R^{15}$; $-NR^{13}CO_2R^{14}$; $-OC(O)R^{13}$; $-OC(O)NR^{13}R^{14}$; $-NR^{13}SOR^{14}$; $-NR^{13}SO_2R^{14}$; $-NR^{13}SONR^{14}R^{15}$; $-NR^{13}SO_2NR^{14}R^{15}$; $-PR^{13}R^{14}$; $-P(O)R^{13}R^{14}$; $-P^+R^{13}R^{14}R^{15}A^-$; $-P(OR^{13})OR^{14}$; $-S^+R^{13}R^{14}A^-$; and $-N^+R^{13}R^{14}R^{15}A^-$; wherein said hydrocarbyl may be optionally substituted with one or more groups comprising one or more heteroatoms, and wherein said hydrocarbyl optionally may have one or more carbon atoms replaced by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen, sulfur and phosphorus;
- [41] wherein R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen or hydrocarbyl, wherein said hydrocarbyl may be optionally substituted with one or more groups comprising one or more heteroatoms, and wherein said hydrocarbyl optionally may have one or more carbon atoms replaced by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen, sulfur and phosphorus; or
- [42] wherein R^{13} and R^{14} together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocyclyl that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy, and quaternary salts; or
- [43] wherein R^{14} and R^{15} together with the nitrogen atom to which they are attached form a cyclic ring; and
- [44] wherein A^- is a pharmaceutically acceptable anion, and M is a pharmaceutically acceptable cation; and

- [45] wherein R^9 is as defined above; and
- [46] one or more R^6 radicals are independently selected from the group consisting of hydrogen; halogen; -CN; -NO₂; hydrocarbyl; - R^5 ; -OR¹³; -NR¹³R¹⁴; -SR¹³; -S(O)R¹³; -S(O)₂R¹³; -SO₃R¹³; -S⁺R¹³R¹⁴A⁻; -NR¹³OR¹⁴; -NR¹³NR¹⁴R¹⁵; - OM; -SO₂OM; -SO₂NR¹³R¹⁴; -NR¹⁴C(O)R¹³; -C(O)OM; -S(O)NR¹³R¹⁴; -N⁺R¹³R¹⁴R¹⁵A⁻; -PR¹³R¹⁴; -P(O)R¹³R¹⁴; -P⁺R¹³R¹⁴R¹⁵A⁻; amino acid residue; peptide residue; polypeptide residue; and carbohydrate residue, wherein said hydrocarbyl may be optionally substituted with one or more groups comprising one or more heteroatoms, and wherein said hydrocarbyl optionally may have one or more carbon atoms replaced by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen, sulfur and phosphorus; and
- [47] wherein R^{13} , R^{14} , R^{15} , A⁻, and M are as defined above; or
- [48] a pharmaceutically acceptable salt, solvate, or prodrug thereof; and
- [49] provided that at least one of R^3 , R^4 and R^6 is R^5 ; and
- [50] provided that at least one of the following conditions is satisfied:
- [51] (a) the R^5 moiety possesses an overall positive charge; and/or
- [52] (b) the R^5 moiety comprises a quaternary ammonium group or a quaternary amine salt; and/or
- [53] (c) the R^5 moiety comprises a phosphonic acid group or at least two carboxyl groups; and/or
- [54] (d) the R^5 moiety comprises a polyethylene glycol group having a molecular weight of at least 1000.

- [55] Preferably, the class of compounds is defined by Formula I wherein:
- [56] j is 0, 1 or 2; and
- [57] m is 0, 1, 2, 3 or 4; and
- [58] R^{1A} and R^{1B} are independently selected from hydrogen and alkyl; and
- [59] R^{2A} and R^{2B} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; or
- [60] R^{2A} and R^{2B} together with the carbon atom to which they are attached form a C_{3-10} cycloalkyl group; and
- [61] one of Z and Y is NR^3 and the other of Z and Y is CHR^4 ;
- [62] wherein R^3 and R^4 are independently selected from the group consisting of hydrogen, oxo, acyl, thioacyl, and R^5 ; and
- [63] wherein R^5 is selected from the group consisting of alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; $-OR^9$; $-SR^9$; $-S(O)R^9$; $-S(O)_2R^9$; and $-SO_3R^9$;
- [64] wherein the R^5 alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; and quaternary heterocyclyl radical is substituted with one or more radicals independently selected from the group consisting of halogen; $-CN$; $-NO_2$; oxo; alkyl; polyalkyl; haloalkyl; hydroxyalkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; $-OR^{13}$; $-NR^{13}R^{14}$; $-SR^{13}$; $-S(O)R^{13}$; $-SO_2R^{13}$; $-SO_3R^{13}$; $-NR^{13}OR^{14}$; $-NR^{13}NR^{14}R^{15}$; $-CO_2R^{13}$; $-OM$; $-SO_2OM$; $-SO_2NR^{13}R^{14}$; $-C(O)NR^{13}R^{14}$; $-C(O)OM$; $-COR^{13}$; $-NR^{13}C(O)R^{14}$; $-NR^{13}C(O)NR^{14}R^{15}$; $-NR^{13}CO_2R^{14}$; $-OC(O)R^{13}$; $-OC(O)NR^{13}R^{14}$; $-NR^{13}SOR^{14}$; $-NR^{13}SO_2R^{14}$; $-NR^{13}SONR^{14}R^{15}$; $-NR^{13}SO_2NR^{14}R^{15}$; $-PR^{13}R^{14}$; $-P(O)R^{13}R^{14}$; $-P^+R^{13}R^{14}R^{15}A^-$; $-P(OR^{13})OR^{14}$; $-S^+R^{13}R^{14}A^-$; and $-N^+R^{13}R^{14}R^{15}A^-$; and

- [65] wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclalkyl, and polyether substituents of the R^5 radical optionally may be further substituted with one or more radicals selected from the group consisting of -CN; halogen; hydroxy; oxo; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclalkyl; quaternary heterocyclyl; $-OR^7$; $-NR^7R^8$; $-SR^7$; $-S(O)R^7$; $-SO_2R^7$; $-SO_3R^7$; $-CO_2R^7$; $-CONR^7R^8$; $-N^+R^7R^8R^9A^-$; $-P(O)R^7R^8$; $-PR^7R^8$; $-P^+R^7R^8R^9A^-$; and $-P(O)(OR^7)OR^8$; and
- [66] wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclalkyl, and polyether substituents of the R^5 radical optionally may have one or more carbons replaced by -O-; $-NR^7$ -; $-N^+R^7R^8A^-$; -S-; -SO-; -SO₂-; $-S^+R^7A^-$; $-PR^7$ -; $-P(O)R^7$ -; $-P^+R^7R^8A^-$; or phenylene; and
- [67] wherein R^7 and R^8 are independently selected from the group consisting of hydrogen; and alkyl; and
- [68] wherein R^9 , R^{10} , and R^W are independently selected from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; alkylammoniumalkyl; arylalkyl; heterocyclalkyl; carboxyalkyl; alkoxyalkyl; carboalkoxyalkyl; carboxyaryl; carboxyheterocyclyl; amino; alkylamino; carboxyalkylamino; alkoxyalkylamino; and acyl; and
- [69] wherein R^{11} and R^{12} are independently selected from the group consisting of hydrogen; -CN; halogen; oxo; alkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclalkyl; carboxyalkyl; alkoxyalkyl; carboalkoxyalkyl; cycloalkyl; cycloalkenyl; haloalkyl; hydroxyalkyl; cyanoalkyl; $-OR^9$; $-NR^9R^{10}$; $-SR^9$; $-S(O)R^9$; $-SO_2R^9$; $-SO_3R^9$; $-CO_2R^9$; and $-CONR^9R^{10}$; or

- [70] R^{11} and R^{12} together with the carbon atom to which they are attached form a cyclic ring; and
- [71] wherein R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether; or
- [72] wherein R^{13} and R^{14} together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocyclyl that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy, and quaternary salts; or
- [73] wherein R^{14} and R^{15} together with the nitrogen atom to which they are attached form a cyclic ring; and
- [74] wherein the R^{13} , R^{14} , and R^{15} alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may be substituted with one or more radicals selected from the group consisting of halogen; -CN; sulfo; oxo; alkyl; haloalkyl; hydroxyalkyl; sulfoalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; quaternary heterocyclylalkyl; carboxy; carboxyalkyl; guanidiny; $-OR^{16}$; $-NR^9R^{10}$; $-N^+R^9R^{10}R^wA^-$; $-SR^{16}$; $-S(O)R^9$; $-SO_2R^9$; $-SO_3R^{16}$; $-CO_2R^{16}$; $-CONR^9R^{10}$; $-SO_2NR^9R^{10}$; $-PO(OR^{16})OR^{17}$; $-P^9R^{10}$;

$-P^+R^9R^{10}R^{11}A^-$; $-S^+R^9R^{10}A^-$; and carbohydrate residue; and

[75] wherein the R^{13} , R^{14} , and R^{15} alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclalkyl; quaternary heterocyclalkyl; alkylarylalkyl; alkylheterocyclalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may have one or more carbons replaced by $-O-$; $-NR^9-$; $-N^+R^9R^{10}A^-$; $-S-$; $-SO-$; $-SO_2-$; $-S^+R^9A^-$; $-PR^9-$; $-P^+R^9R^{10}A^-$; $-P(O)R^9-$; phenylene; carbohydrate residue; amino acid residue; peptide residue; or polypeptide residue; and

[76] wherein R^{16} and R^{17} are independently selected from the group consisting of R^9 and M; and

[77] wherein A is a pharmaceutically acceptable cation and M is a pharmaceutically acceptable cation; and

[78] one or more R^6 radicals are independently selected from the group consisting of R^5 , hydrogen; halogen; $-CN$; $-NO_2$; alkyl; cycloalkyl; polyalkyl; haloalkyl; hydroxyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclalkyl; polyether; acyloxy; $-OR^{13}$; $-NR^{13}R^{14}$; $-SR^{13}$; $-S(O)R^{13}$; $-S(O)_2R^{13}$; $-SO_3R^{13}$; $-S^+R^{13}R^{14}A^-$; $-NR^{13}OR^{14}$; $-NR^{13}NR^{14}R^{15}$; $-CO_2R^{13}$; $-OM$; $-SO_2OM$; $-SO_2NR^{13}R^{14}$; $-NR^{14}C(O)R^1$; $-C(O)NR^{13}R^{14}$; $-C(O)OM$; $-COR^{13}$; $-OR^{18}$; $-S(O)_nNR^{13}R^{14}$; $-NR^{13}R^{18}$; $-NR^{18}OR^{14}$; $-N^+R^{13}R^{14}R^{15}A^-$; $-PR^{13}R^{14}$; $-P(O)R^{13}R^{14}$; $-P^+R^{13}R^{14}R^{15}A^-$; amino acid residue; peptide residue; polypeptide residue; and carbohydrate residue;

[79] wherein the R^6 alkyl; cycloalkyl; polyalkyl; haloalkyl; hydroxyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclalkyl; polyether; acyloxy radicals optionally may be further substituted with one or more radicals

selected from the group consisting of halogen; -CN; oxo; -OR¹⁶; -NR⁹R¹⁰; -N⁺R⁹R¹⁰R^wA⁻; -SR¹⁶;

[80] -S(O)R⁹; -SO₂R⁹; -SO₃R¹⁶; -CO₂R¹⁶; -CONR⁹R¹⁰; -SO₂NR⁹R¹⁰;

-PO(OR¹⁶)OR¹⁷; -P⁹R¹⁰; -P⁺R⁹R¹¹R¹²A⁻; -S⁺R⁹R¹⁰A⁻; and carbohydrate residue; and

[81] wherein the R⁶ quaternary heterocyclyl radical optionally may be substituted with one or more radicals selected from the group consisting of halogen; -CN; -NO₂; oxo; alkyl; cycloalkyl; polyalkyl; haloalkyl; hydroxyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; -OR¹³; -NR¹³R¹⁴; -SR¹³; -S(O)R¹³; -SO₂R¹³; -SO₃R¹³; -NR¹³OR¹⁴; -NR¹³NR¹⁴R¹⁵; -CO₂R¹³; OM; -SO₂OM; -SO₂NR¹³R¹⁴; -C(O)NR¹³R¹⁴; -C(O)OM; -COR¹³; -P(O)R¹³R¹⁴; -P¹³R¹⁴; -P⁺R¹³R¹⁴R¹⁵A⁻; -P(OR¹³)OR¹⁴; -S⁺R¹³R¹⁴A⁻; -N⁺R¹³R¹⁴R¹⁵A⁻; and carbohydrate residue; and

[82] wherein the R⁶ radicals comprising carbon optionally may have one or more carbons replaced by -O-; -NR¹³-; -N⁺R¹³R¹⁴A⁻; -S-; -SO-; -SO₂-; -S⁺R¹³A⁻; -PR¹³-; -P(O)R¹³-; -PR¹³R¹⁴; -P⁺R¹³R¹⁴A⁻; phenylene; amino acid residue; peptide residue; polypeptide residue; carbohydrate residue; polyether; or polyalkyl; wherein said phenylene; amino acid residue; peptide residue; polypeptide residue; carbohydrate residue; and polyalkyl optionally may have one or more carbons replaced by -O-; -NR⁹-; -N⁺R⁹R¹⁰A⁻; -S-; -SO-; -SO₂-; -S⁺R⁹A⁻; -PR⁹-; -P⁺R⁹R¹⁰A⁻; or -P(O)R⁹-; and

[83] wherein R¹⁸ is selected from the group consisting of alkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; acyl; alkoxycarbonyl; arylalkoxycarbonyl; and heterocyclylalkoxycarbonyl; and

- [84] wherein the R^{18} alkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclalkyl; acyl; alkoxycarbonyl; arylalkoxycarbonyl; and heterocyclalkoxycarbonyl radicals optionally may be substituted with one or more radicals selected from the group consisting of halogen; -CN; NO_2 ; oxo; $-\text{OR}^9$; $-\text{NR}^9\text{R}^{10}$; $-\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$; $-\text{SR}^9$; $-\text{S}(\text{O})\text{R}^9$; $-\text{SO}_2\text{R}^9$; $-\text{SO}_3\text{R}^9$; $-\text{CO}_2\text{R}^9$; $-\text{CONR}^9\text{R}^{10}$; $-\text{SO}_2\text{OM}$; $-\text{SO}_2\text{NR}^9\text{R}^{10}$; $-\text{PR}^9\text{R}^{10}$; $-\text{P}(\text{OR}^{13})\text{OR}^{14}$; $-\text{PO}(\text{OR}^{16})\text{OR}^{17}$; and $-\text{C}(\text{O})\text{OM}$; or
- [85] a pharmaceutically acceptable salt, solvate, or prodrug thereof;
- [86] provided that at least one of R^3 , R^4 and R^6 is R^5 ; and
- [87] provided that at least one of the following conditions is satisfied:
- [88] (a) the R^5 moiety possesses an overall positive charge; and/or
- [89] (b) the R^5 moiety comprises a quaternary ammonium group or a quaternary amine salt; and/or
- [90] (c) the R^5 moiety comprises a phosphonic acid group or at least two carboxyl groups; and/or
- [91] (d) the R^5 moiety comprises a polyethylene glycol group having a molecular weight of at least 1000.
- [92] In one embodiment of the compounds of Formula I, R^5 is aryl substituted with one or more radicals independently selected from the group consisting of halogen; -CN; $-\text{NO}_2$; oxo; alkyl; polyalkyl; haloalkyl; hydroxyalkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclalkyl; polyether; $-\text{OR}^{13}$; $-\text{NR}^{13}\text{R}^{14}$; $-\text{SR}^{13}$; $-\text{S}(\text{O})\text{R}^{13}$; $-\text{SO}_2\text{R}^{13}$; $-\text{SO}_3\text{R}^{13}$; $-\text{NR}^{13}\text{OR}^{14}$; $-\text{NR}^{13}\text{NR}^{14}\text{R}^{15}$; $-\text{CO}_2\text{R}^{13}$; -OM; $-\text{SO}_2\text{OM}$; $-\text{SO}_2\text{NR}^{13}\text{R}^{14}$; $-\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$; $-\text{C}(\text{O})\text{OM}$; $-\text{COR}^{13}$; $-\text{NR}^{13}\text{C}(\text{O})\text{R}^{14}$; $-\text{NR}^{13}\text{C}(\text{O})\text{NR}^{14}\text{R}^{15}$; $-\text{NR}^{13}\text{CO}_2\text{R}^{14}$; $-\text{OC}(\text{O})\text{R}^{13}$; $-\text{OC}(\text{O})\text{NR}^{13}\text{R}^{14}$; $-\text{NR}^{13}\text{SOR}^{14}$; $-\text{NR}^{13}\text{SO}_2\text{R}^{14}$; $-\text{NR}^{13}\text{SONR}^{14}\text{R}^{15}$; $-\text{NR}^{13}\text{SO}_2\text{NR}^{14}\text{R}^{15}$; $-\text{PR}^{13}\text{R}^{14}$; $-\text{P}(\text{O})\text{R}^{13}\text{R}^{14}$

cycloalkyl; cycloalkenyl; haloalkyl; hydroxyalkyl; cyanoalkyl; -OR⁹; -NR⁹R¹⁰; -SR⁹; -S(O)R⁹; -SO₂R⁹; -SO₃R⁹; -CO₂R⁹; and -CONR⁹R¹⁰; or

[98] R¹¹ and R¹² together with the carbon atom to which they are attached form a cyclic ring; and

[99] wherein R¹³, R¹⁴, and R¹⁵ are independently selected from the group consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether; or

[100] wherein R¹³ and R¹⁴ together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocyclyl that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy, and quaternary salts; or

[101] wherein R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form a cyclic ring; and

[102] wherein the R¹³, R¹⁴, and R¹⁵ alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may be substituted with one or more radicals selected from the group consisting of halogen; -CN; sulfo; oxo; alkyl; haloalkyl; hydroxyalkyl; sulfoalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; quaternary heterocyclylalkyl; carboxy; carboxyalkyl; guanidiny; -OR¹⁶; -NR⁹R¹⁰; -N⁺

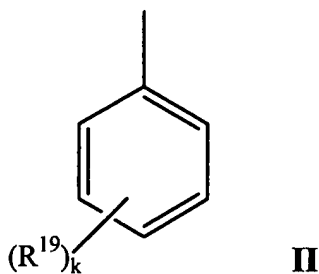
$R^9R^{10}R^wA^-$; $-SR^{16}$; $-S(O)R^9$; $-SO_2R^9$; $-SO_3R^{16}$; $-CO_2R^{16}$; $-CONR^9R^{10}$; $-SO_2NR^9R^{10}$; $-PO(OR^{16})OR^{17}$; $-P^9R^{10}$; $-P^+R^9R^{10}R^{11}A^-$; $-S^+R^9R^{10}A^-$; and carbohydrate residue; and

[103] wherein the R^{13} , R^{14} , and R^{15} alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclalkyl; quaternary heterocyclalkyl; alkylarylalkyl; alkylheterocyclalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may have one or more carbons replaced by $-O-$; $-NR^9-$; $-N^+R^9R^{10}A^-$; $-S-$; $-SO-$; $-SO_2-$; $-S^+R^9A^-$; $-PR^9-$; $-P^+R^9R^{10}A^-$; $-P(O)R^9$; phenylene; carbohydrate residue; amino acid residue; peptide residue; or polypeptide residue; and

[104] wherein R^{16} and R^{17} are independently selected from the group consisting of R^9 and M; and

[105] wherein A is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation.

[106] In another embodiment of the compounds of Formula I, R^5 is:



[107] wherein

[108] k is 0, 1, 2, 3 or 4; and

- [109] one or more R^{19} are independently selected from the group consisting of halogen; -CN; -NO₂; oxo; alkyl; polyalkyl; haloalkyl; hydroxyalkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; -OR¹³; -NR¹³R¹⁴; -SR¹³; -S(O)R¹³; -SO₂R¹³; -SO₃R¹³; -NR¹³OR¹⁴; -NR¹³NR¹⁴R¹⁵; -CO₂R¹³; -OM; -SO₂OM; -SO₂NR¹³R¹⁴; -C(O)NR¹³R¹⁴; -C(O)OM; -COR¹³; -NR¹³C(O)R¹⁴; -NR¹³C(O)NR¹⁴R¹⁵; -NR¹³CO₂R¹⁴; -OC(O)R¹³; -OC(O)NR¹³R¹⁴; -NR¹³SOR¹⁴; -NR¹³SO₂R¹⁴; -NR¹³SONR¹⁴R¹⁵; -NR¹³SO₂NR¹⁴R¹⁵; -PR¹³R¹⁴; -P(O)R¹³R¹⁴; -P⁺R¹³R¹⁴R¹⁵A⁻; -P(OR¹³)OR¹⁴; -S⁺R¹³R¹⁴A⁻; and -N⁺R¹³R¹⁴R¹⁵A⁻; and
- [110] wherein the R^{19} alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether radicals optionally may be further substituted with one or more radicals selected from the group consisting of -CN; halogen; hydroxy; oxo; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclyl; -OR⁷; -NR⁷R⁸; -SR⁷; -S(O)R⁷; -SO₂R⁷; -SO₃R⁷; -CO₂R⁷; -CONR⁷R⁸; -N⁺R⁷R⁸R⁹A⁻; -P(O)R⁷R⁸; -PR⁷R⁸; -P⁺R⁷R⁸R⁹A⁻; and -P(O)(OR⁷)OR⁸; and
- [111] wherein the R^{19} alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether radicals optionally may have one or more carbons replaced by -O-; -NR⁷-; -N⁺R⁷R⁸A⁻; -S-; -SO-; -SO₂-; -S⁺R⁷A⁻; -PR⁷-; -P(O)R⁷-; -P⁺R⁷R⁸A⁻; or phenylene; and
- [112] wherein R^7 and R^8 are independently selected from the group consisting of hydrogen; and alkyl; and

- [113] wherein R^9 , R^{10} , and R^W are independently selected from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; alkylammoniumalkyl; arylalkyl; heterocyclalkyl; carboxyalkyl; alkoxyalkyl; carboalkoxyalkyl; carboxyaryl; carboxyheterocyclyl; amino; alkylamino; carboxyalkylamino; alkoxyalkylamino; and acyl; and
- [114] wherein R^{11} and R^{12} are independently selected from the group consisting of hydrogen; -CN; halogen; oxo; alkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclalkyl; carboxyalkyl; alkoxyalkyl; carboalkoxyalkyl; cycloalkyl; cycloalkenyl; haloalkyl; hydroxyalkyl; cyanoalkyl; $-OR^9$; $-NR^9R^{10}$; $-SR^9$; $-S(O)R^9$; $-SO_2R^9$; $-SO_3R^9$; $-CO_2R^9$; and $-CONR^9R^{10}$; or
- [115] R^{11} and R^{12} together with the carbon atom to which they are attached form a cyclic ring; and
- [116] wherein R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclalkyl; quaternary heterocyclalkyl; alkylarylalkyl; alkylheterocyclalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether; or
- [117] wherein R^{13} and R^{14} together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocyclyl that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy, and quaternary salts; or
- [118] wherein R^{14} and R^{15} together with the nitrogen atom to which they are attached form a cyclic ring; and
- [119] wherein the R^{13} , R^{14} , and R^{15} alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl;

heterocyclalkyl; quaternary heterocyclalkyl; alkylalkyl;
 alkylheterocyclalkyl; alkylammoniumalkyl; aminoalkyl;
 aminocarbonylalkyl; alkylaminocarbonylalkyl;
 carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may be
 substituted with one or more radicals selected from the group consisting of
 halogen; -CN; sulfo; oxo; alkyl; haloalkyl; hydroxyalkyl; sulfoalkyl; alkenyl;
 alkynyl; aryl; heterocycl; quaternary heterocycl; quaternary
 heterocyclalkyl; carboxy; carboxyalkyl; guanidiny; -OR¹⁶; -NR⁹R¹⁰; -N⁺
 R⁹R¹⁰R^wA⁻; -SR¹⁶; -S(O)R⁹; -SO₂R⁹; -SO₃R¹⁶; -CO₂R¹⁶; -CONR⁹R¹⁰; -
 SO₂NR⁹R¹⁰; -PO(OR¹⁶)OR¹⁷; -P⁹R¹⁰; -P⁺R⁹R¹⁰R¹¹A⁻; -S⁺R⁹R¹⁰A⁻;
 and carbohydrate residue; and

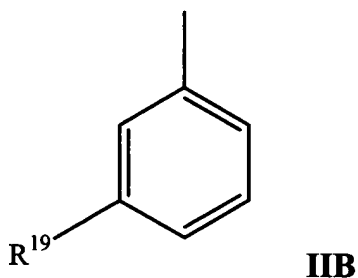
[120] wherein the R¹³, R¹⁴, and R¹⁵ alkyl; haloalkyl; cycloalkyl; polyalkyl;
 alkenyl; alkynyl; aryl; heterocycl; quaternary heterocycl; arylalkyl;
 heterocyclalkyl; quaternary heterocyclalkyl; alkylalkyl;
 alkylheterocyclalkyl; alkylammoniumalkyl; aminoalkyl;
 aminocarbonylalkyl; alkylaminocarbonylalkyl;
 carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may have
 one or more carbons replaced by -O-; -NR⁹-; -N⁺R⁹R¹⁰A⁻; -S-; -SO-; -SO₂-;
 -S⁺R⁹A⁻; -PR⁹-; -P⁺R⁹R¹⁰A⁻; -P(O)R⁹-; phenylene; carbohydrate residue;
 amino acid residue; peptide residue; or polypeptide residue; and

[121] wherein R¹⁶ and R¹⁷ are independently selected from the group consisting of
 R⁹ and M; and

[122] wherein A is a pharmaceutically acceptable anion and M is a pharmaceutically
 acceptable cation.

[123] In another embodiment, R⁵ is:

[125] In another embodiment, R^5 is:



[127] In another embodiment:

[128] R¹⁹ is independently selected from the group consisting of -OR¹³, -NR¹³R¹⁴, -NR¹³C(O)R¹⁴, -OC(O)NR¹³R¹⁴, and -NR¹³SO₂R¹⁴, and

[129] wherein R¹³, R¹⁴, and R¹⁵ are independently selected from the group consisting of alkyl, polyether, aryl, quaternary heterocycle, arylalkyl,

heterocyclalkyl, quaternary heterocyclalkyl, alkylheterocyclalkyl, and alkylammoniumalkyl,

[130] wherein alkyl optionally has one or more carbons replaced by O or $N^+R^9R^{10}A^-$, and

[131] wherein R^{13} , R^{14} , and R^{15} are optionally substituted with one or more groups selected from the group consisting of hydroxy, carboxy, alkyl, quaternary heterocyclalkyl, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$, $-S(O)_3R^9$, $-NR^9R^{10}$, $-N^+R^9R^{11}R^{12}A^-$, $-CONR^9R^{10}$, and $-PO(OR^{16})OR^{17}$, and

[132] wherein R^9 and R^{10} are independently selected from the group consisting of hydrogen, alkyl, heterocyclalkyl, carboxyalkyl, carboalkoxyalkyl, and carboxyalkylheterocycle; and

[133] wherein R^{11} and R^{12} are independently alkyl; and

[134] wherein A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation.

[135] In another embodiment:

[136] R^{19} is independently selected from the group consisting of $-OR^{13}$, $-NR^{13}R^{14}$, $-NR^{13}C(O)R^{14}$, $-OC(O)NR^{13}R^{14}$, and $-NR^{13}SO_2R^{14}$, and

[137] wherein R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of polyether, aryl, quaternary heterocycle, arylalkyl, heterocyclalkyl, quaternary heterocyclalkyl, and alkylheterocyclalkyl,

[138] wherein R^{13} , R^{14} , and R^{15} are optionally substituted with one or more groups selected from the group consisting of hydroxy, carboxy, alkyl, quaternary heterocyclalkyl, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$, $-S(O)_3R^9$, $-NR^9R^{10}$, $-N^+R^9R^{11}R^{12}A^-$, $-CONR^9R^{10}$, and $-PO(OR^{16})OR^{17}$, and

[139] wherein R⁹ and R¹⁰ are independently selected from the group consisting of hydrogen, alkyl, heterocyclalkyl, carboxyalkyl, carboalkoxyalkyl, and carboxyalkylheterocycle; and

[140] wherein R¹¹ and R¹² are independently alkyl; and

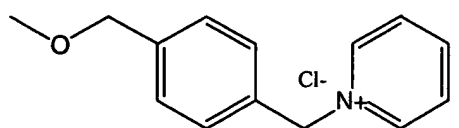
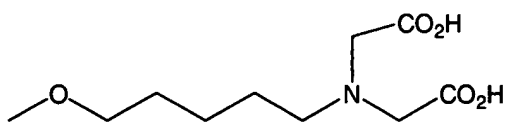
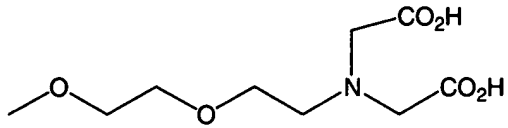
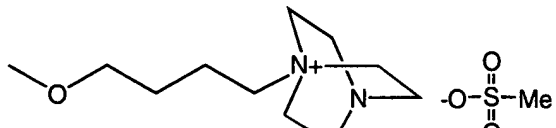
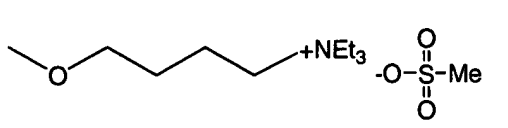
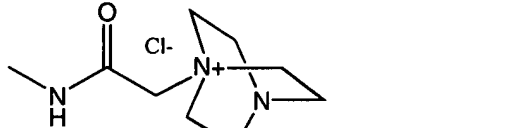
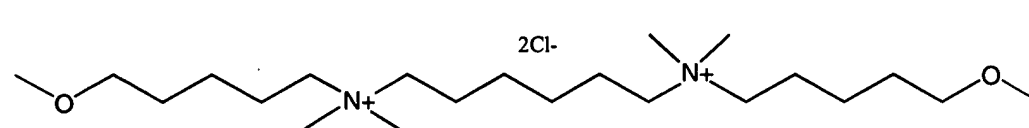
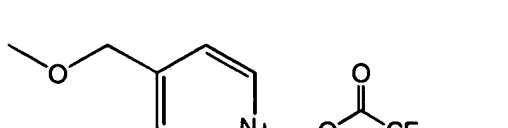
[141] wherein A⁻ is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation.

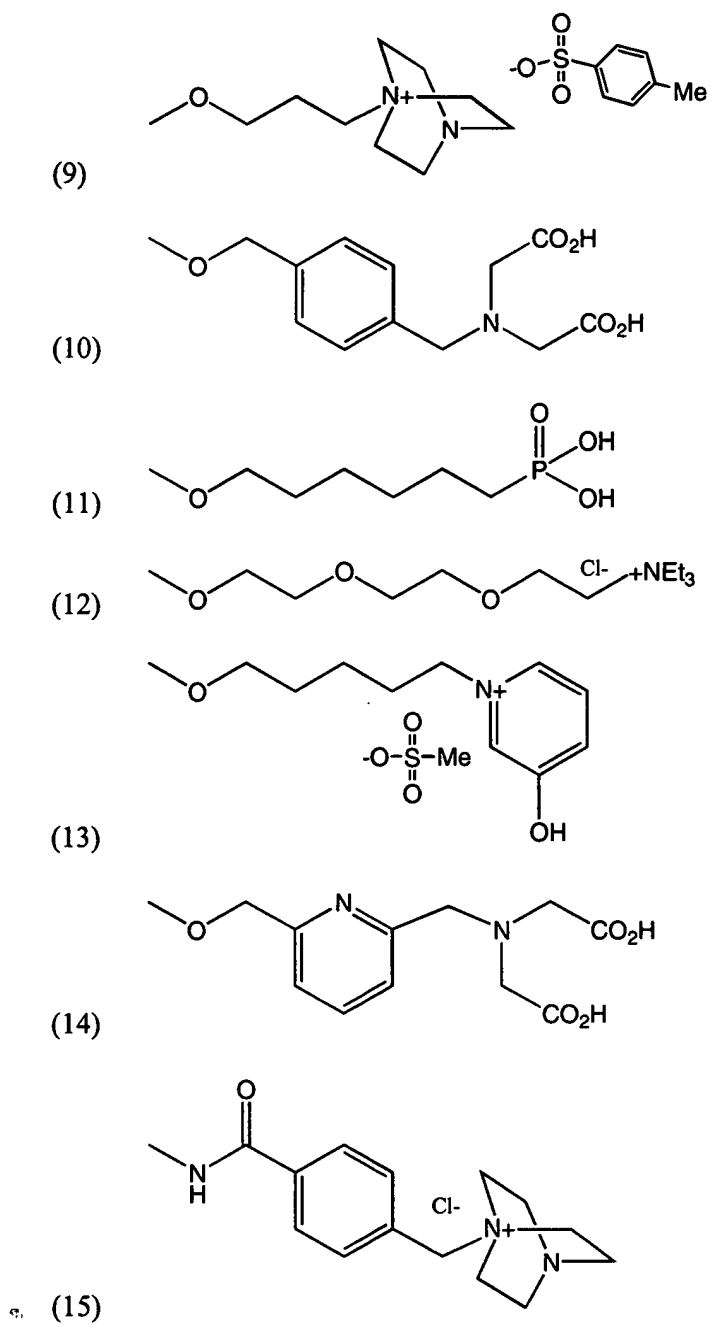
[142] In another embodiment, R¹⁹ is selected from the group consisting of:

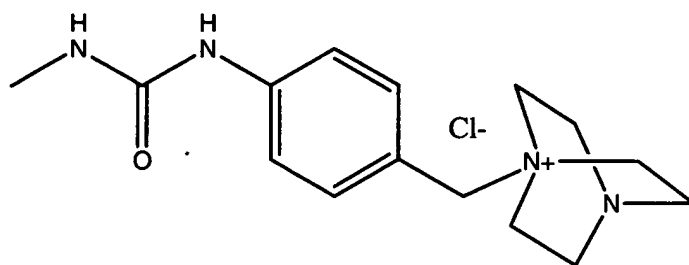
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TABLE 1

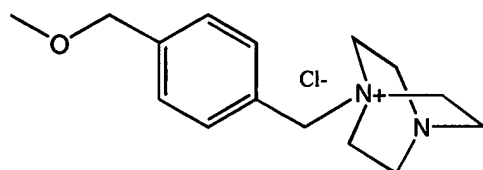
R¹⁹

- (1) 
- (2) 
- (3) 
- (4) 
- (5) 
- (6) 
- (7) 
- (8) 

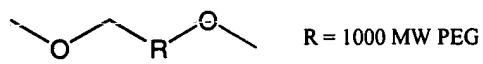




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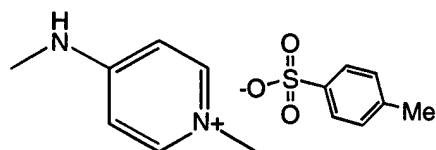


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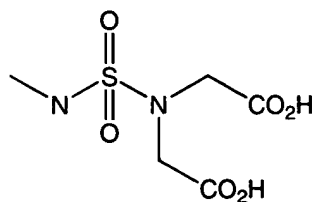


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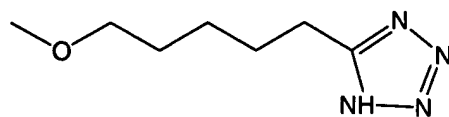
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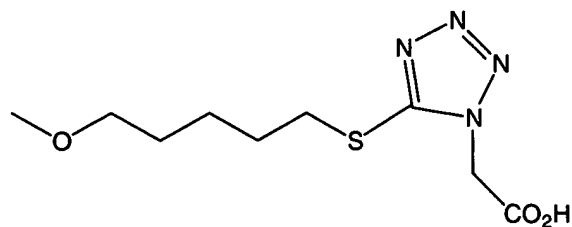
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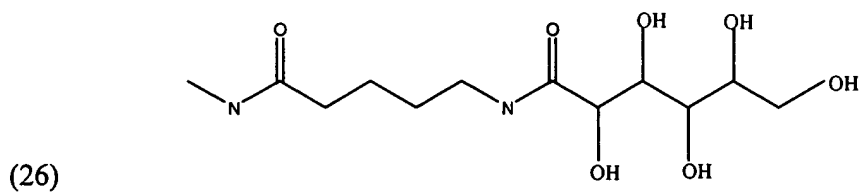
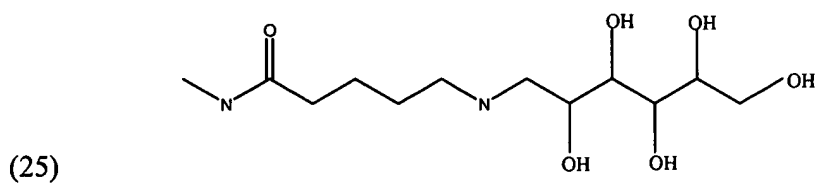
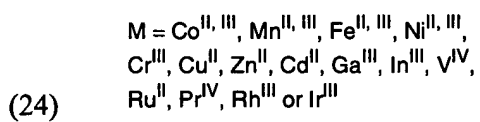
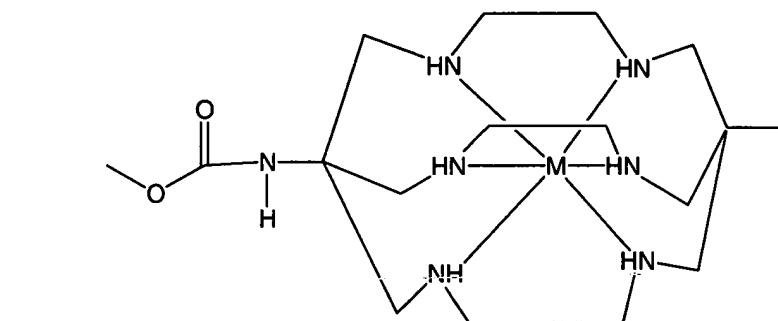
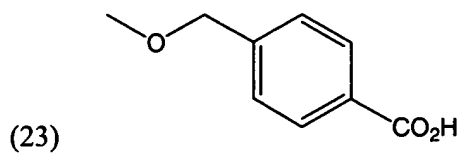
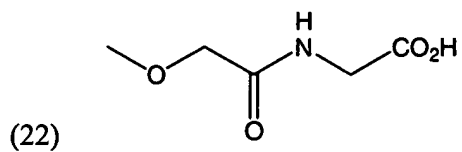
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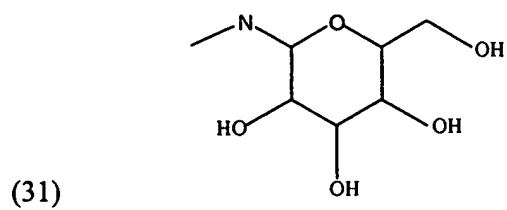
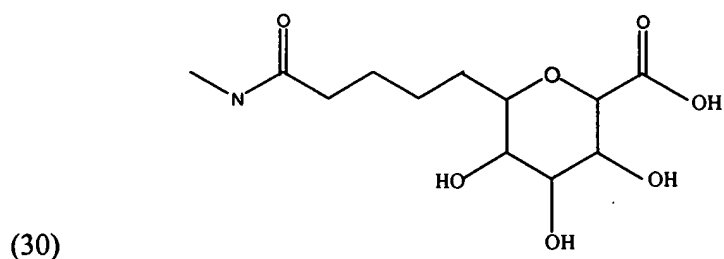
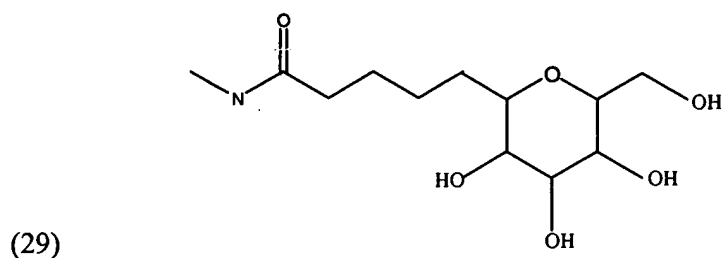
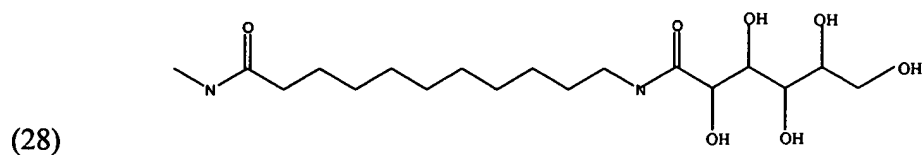
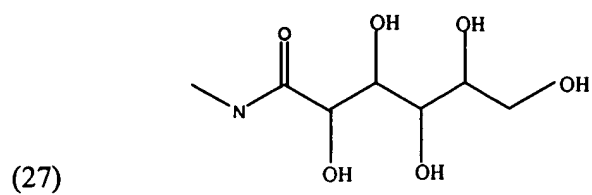


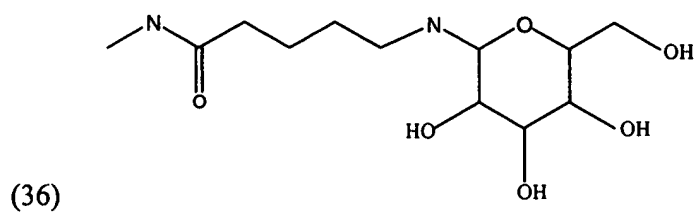
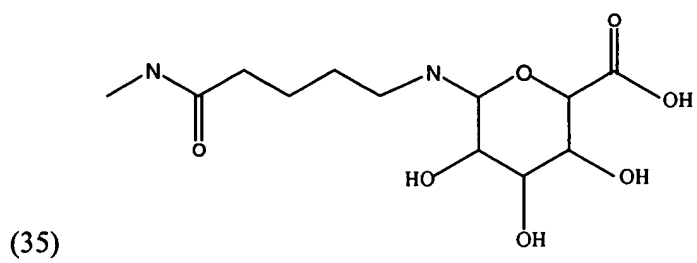
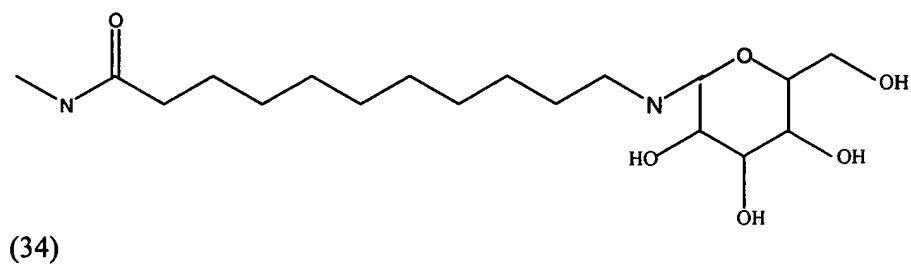
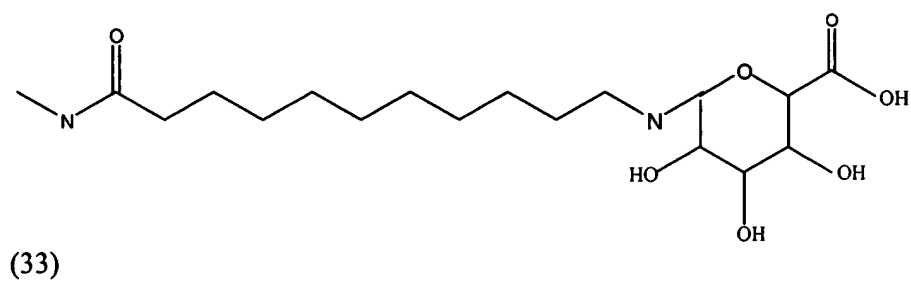
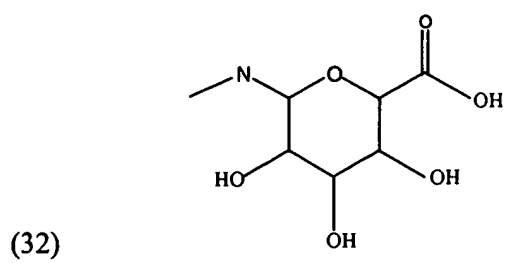
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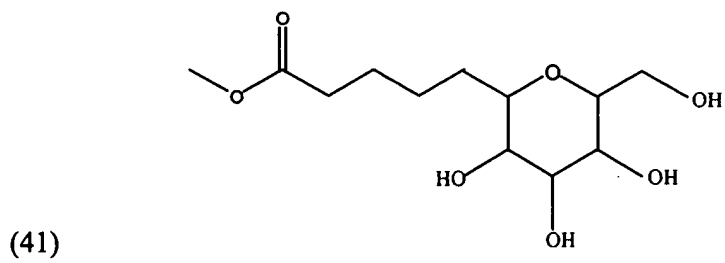
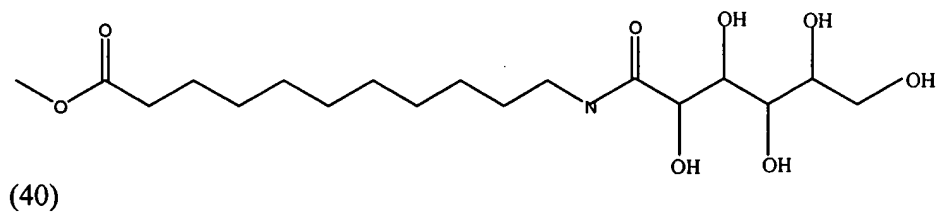
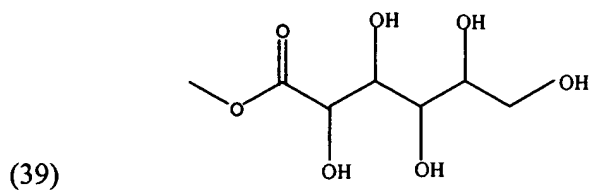
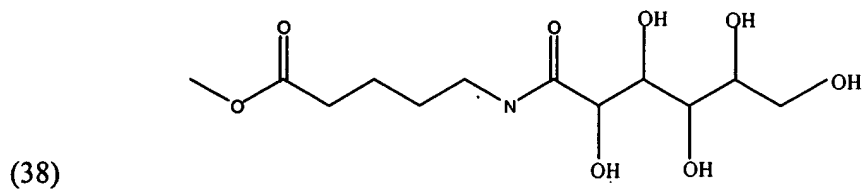
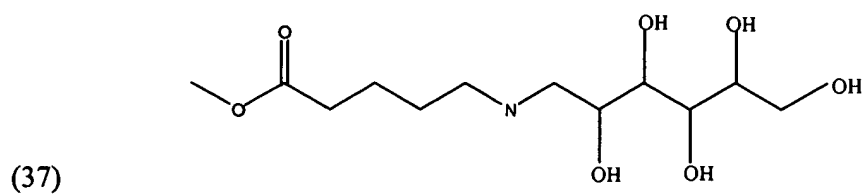


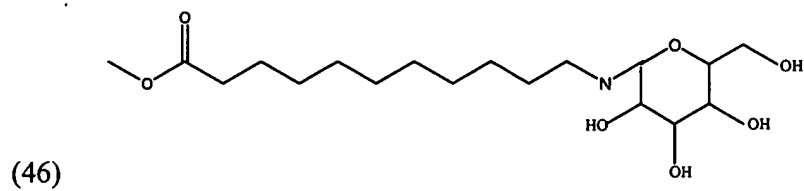
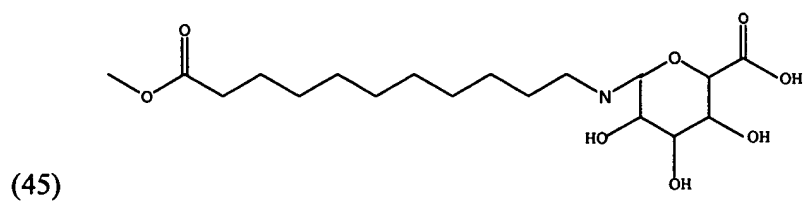
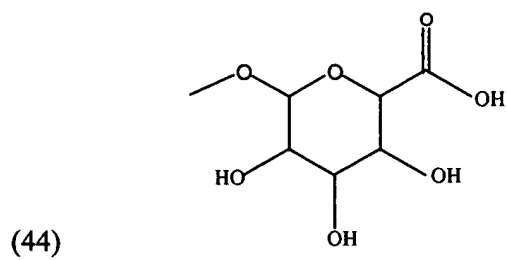
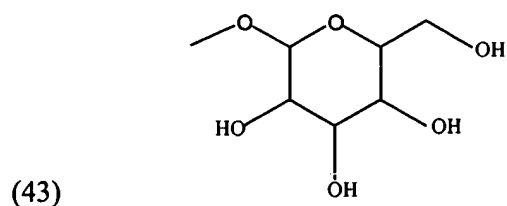
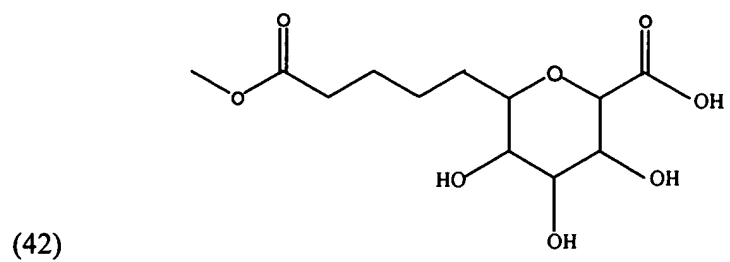
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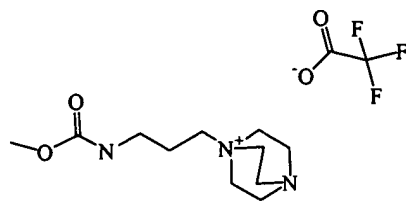
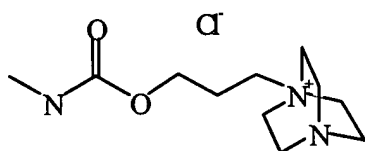
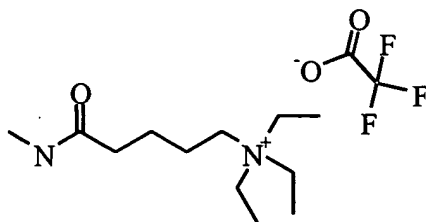
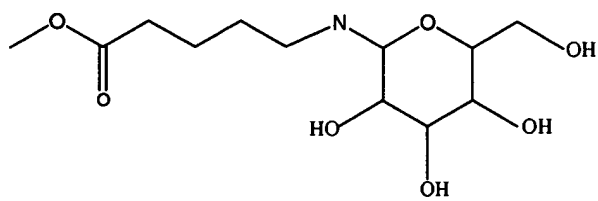
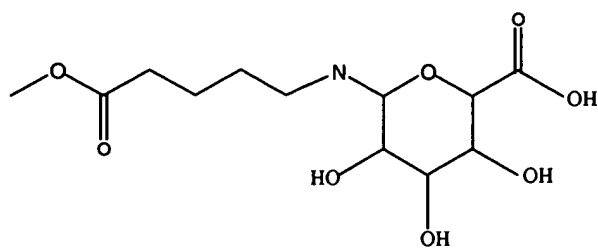


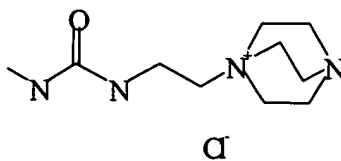




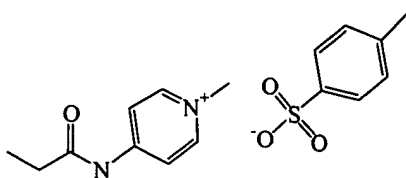




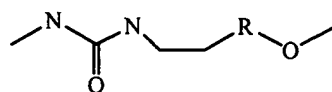




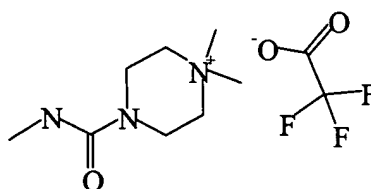
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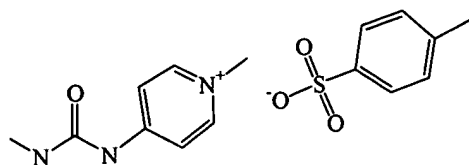
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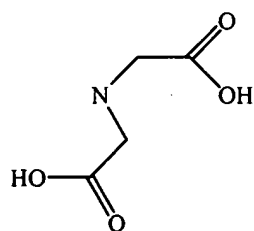
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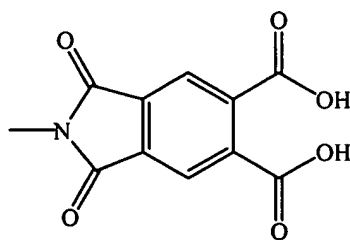
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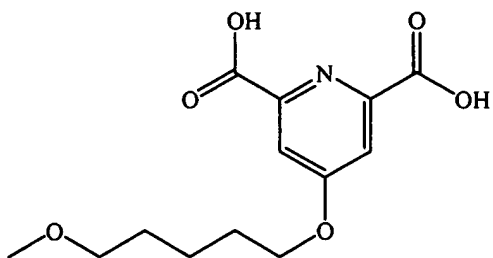


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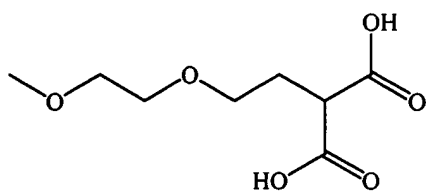


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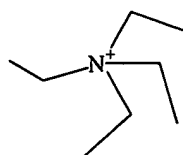


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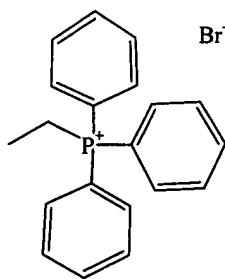
Γ^-

(62)

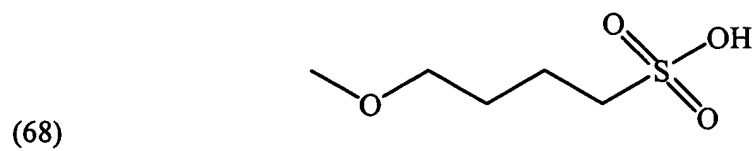
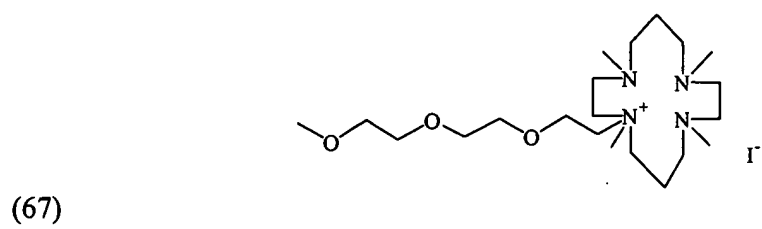
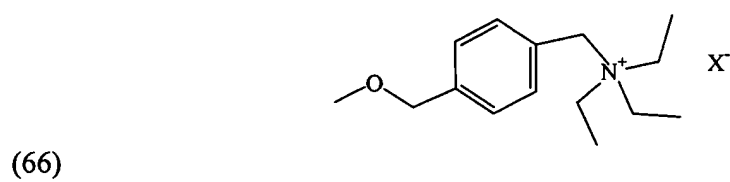
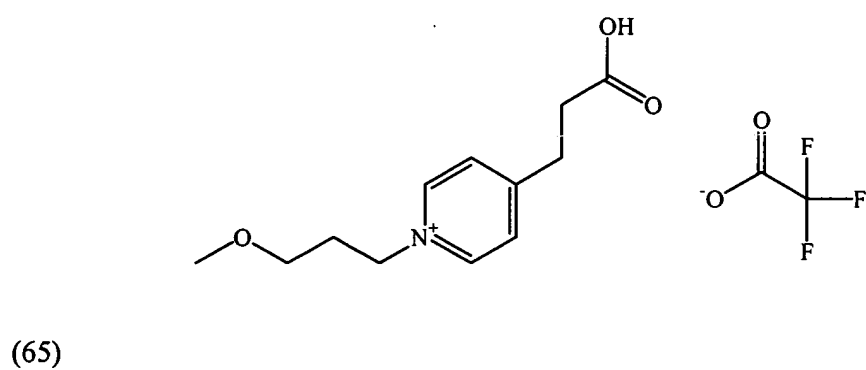
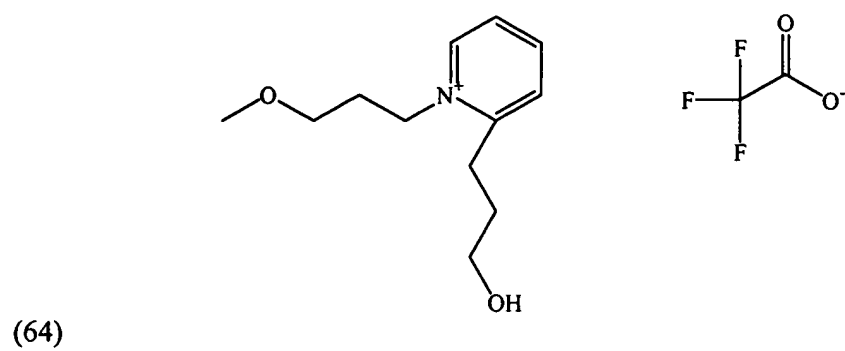


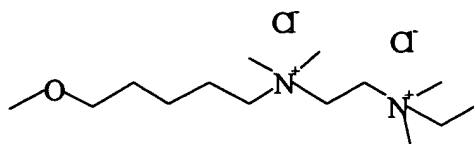
Br^-

(63)

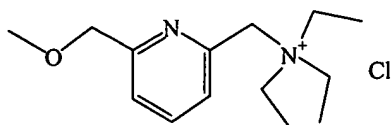


Br^-





(69)



(70)

[143] Optionally, R^{19} may be selected from the following: (1) – (24), (25) – (48) or (49) – (70) from Table 1. Further, R^{19} may be acidic or contain a quaternary ammonium nitrogen. Even further, R^{19} may be selected from the following: (1) – (5), (6) – (10), (11) – (15), (16) – (20), (21) – (25), (26) – (30), (31) – (35), (36) – (40), (41) – (45), (46) – (50), (51) – (55), (56) – (60), (61) – (65), (66) – (70), or combinations thereof.

[144] In another embodiment of the compounds of Formula I, R^3 is R^5 ; and

[145] R^4 is selected from the group consisting of hydrogen and alkyl.

[146] In another embodiment of the compounds of Formula I, R^3 is selected from the group consisting of hydrogen and alkyl; and R^4 is R^5 .

[147] In another embodiment of the compounds of Formula I:

[148] R^3 is R^5 ; and

[149] R^4 is selected from the group consisting of hydrogen; oxo; alkyl; cycloalkyl; aryl; heterocyclyl; acyl, thioacyl, and $-OR^9$;

[150] wherein the R^4 alkyl; cycloalkyl; aryl; heterocyclyl radical is substituted with one or more radicals independently selected from the group consisting of halogen; $-CN$; $-NO_2$; oxo; alkyl; polyalkyl; haloalkyl; hydroxyalkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; $-OR^{13}$; $-NR^{13}R^{14}$; $-SR^{13}$; $-S(O)R^{13}$; $-SO_2R^{13}$; $-SO_3R^{13}$; $-NR^{13}OR^{14}$; $-NR^{13}NR^{14}R^{15}$; $-CO_2R^{13}$; $-OM$; $-SO_2$

OM; $-\text{SO}_2\text{NR}^{13}\text{R}^{14}$; $-\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$; $-\text{C}(\text{O})\text{OM}$; $-\text{COR}^{13}$; $-\text{NR}^{13}\text{C}(\text{O})\text{R}^{14}$; $-\text{NR}^{13}\text{C}(\text{O})\text{NR}^{14}\text{R}^{15}$; $-\text{NR}^{13}\text{CO}_2\text{R}^{14}$; $-\text{OC}(\text{O})\text{R}^{13}$; $-\text{OC}(\text{O})\text{NR}^{13}\text{R}^{14}$; $-\text{NR}^{13}\text{SOR}^{14}$; $-\text{NR}^{13}\text{SO}_2\text{R}^{14}$; $-\text{NR}^{13}\text{SONR}^{14}\text{R}^{15}$; $-\text{NR}^{13}\text{SO}_2\text{NR}^{14}\text{R}^{15}$; $-\text{PR}^{13}\text{R}^{14}$; $-\text{P}(\text{O})\text{R}^{13}\text{R}^{14}$; $-\text{P}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$; $-\text{P}(\text{OR}^{13})\text{OR}^{14}$; $-\text{S}^+\text{R}^{13}\text{R}^{14}\text{A}^-$; and $-\text{N}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$; and

- [151] wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether substituents of the R^4 radical optionally may be further substituted with one or more radicals selected from the group consisting of $-\text{CN}$; halogen; hydroxy; oxo; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclyl; $-\text{OR}^7$; $-\text{NR}^7\text{R}^8$; $-\text{SR}^7$; $-\text{S}(\text{O})\text{R}^7$; $-\text{SO}_2\text{R}^7$; $-\text{SO}_3\text{R}^7$; $-\text{CO}_2\text{R}^7$; $-\text{CONR}^7\text{R}^8$; $-\text{N}^+\text{R}^7\text{R}^8\text{R}^9\text{A}^-$; $-\text{P}(\text{O})\text{R}^7\text{R}^8$; $-\text{PR}^7\text{R}^8$; $-\text{P}^+\text{R}^7\text{R}^8\text{R}^9\text{A}^-$; and

$-\text{P}(\text{O})(\text{OR}^7)\text{OR}^8$; and

- [152] wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether substituents of the R^4 radical optionally may have one or more carbons replaced by

$-\text{O}-$; $-\text{NR}^7-$; $-\text{N}^+\text{R}^7\text{R}^8\text{A}^-$; $-\text{S}-$; $-\text{SO}-$; $-\text{SO}_2-$; $-\text{S}^+\text{R}^7\text{A}^-$; $-\text{PR}^7-$; $-\text{P}(\text{O})\text{R}^7-$;

$-\text{P}^+\text{R}^7\text{R}^8\text{A}^-$; or phenylene; and

- [153] wherein R^7 and R^8 are independently selected from the group consisting of hydrogen; and alkyl; and

- [154] wherein R^9 , R^{10} , and R^w are independently selected from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl;

alkylammoniumalkyl; arylalkyl; heterocyclalkyl; carboxyalkyl; alkoxyalkyl; carboalkoxyalkyl; carboxyaryl; carboxyheterocycl; amino; alkylamino; carboxyalkylamino; alkoxyalkylamino; and acyl; and

[155] wherein R^{11} and R^{12} are independently selected from the group consisting of hydrogen; -CN; halogen; oxo; alkyl; alkenyl; alkynyl; aryl; heterocycl; arylalkyl; heterocyclalkyl; carboxyalkyl; alkoxyalkyl; carboalkoxyalkyl; cycloalkyl; cycloalkenyl; haloalkyl; hydroxyalkyl; cyanoalkyl; $-OR^9$; $-NR^9R^{10}$; $-SR^9$; $-S(O)R^9$; $-SO_2R^9$; $-SO_3R^9$; $-CO_2R^9$; and $-CONR^9R^{10}$; or

[156] R^{11} and R^{12} together with the carbon atom to which they are attached form a cyclic ring; and

[157] wherein R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocycl; quaternary heterocycl; arylalkyl; heterocyclalkyl; quaternary heterocyclalkyl; alkylarylalkyl; alkylheterocyclalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether; or

[158] wherein R^{13} and R^{14} together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycl that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy, and quaternary salts; or

[159] wherein R^{14} and R^{15} together with the nitrogen atom to which they are attached form a cyclic ring; and

[160] wherein the R^{13} , R^{14} , and R^{15} alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocycl; quaternary heterocycl; arylalkyl; heterocyclalkyl; quaternary heterocyclalkyl; alkylarylalkyl; alkylheterocyclalkyl; alkylammoniumalkyl; aminoalkyl;

aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may be substituted with one or more radicals selected from the group consisting of halogen; -CN; sulfo; oxo; alkyl; haloalkyl; hydroxyalkyl; sulfoalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; quaternary heterocyclylalkyl; carboxy; carboxyalkyl; guanidiny; -OR¹⁶; -NR⁹R¹⁰; -N⁺R⁹R¹⁰R^wA⁻; -SR¹⁶; -S(O)R⁹; -SO₂R⁹; -SO₃R¹⁶; -CO₂R¹⁶; -CONR⁹R¹⁰; -SO₂NR⁹R¹⁰; -PO(OR¹⁶)OR¹⁷; -P⁹R¹⁰; -P⁺R⁹R¹⁰R¹¹A⁻; -S⁺R⁹R¹⁰A⁻; and carbohydrate residue; and

[161] wherein the R¹³, R¹⁴, and R¹⁵ alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may have one or more carbons replaced by -O-; -NR⁹; -N⁺R⁹R¹⁰A⁻; -S-; -SO-; -SO₂-; -S⁺R⁹A⁻; -PR⁹-; -P⁺R⁹R¹⁰A⁻; -P(O)R⁹; phenylene; carbohydrate residue; amino acid residue; peptide residue; or polypeptide residue; and

[162] wherein R¹⁶ and R¹⁷ are independently selected from the group consisting of R⁹ and M; and

[163] wherein A is a pharmaceutically acceptable cation and M is a pharmaceutically acceptable cation.

[164] In another embodiment of the compounds of Formula I:

[165] R³ is selected from the group consisting of hydrogen; oxo; alkyl; cycloalkyl; aryl; heterocyclyl; acyl, thioacyl, and -OR⁹;

[166] wherein the R^3 alkyl; cycloalkyl; aryl; heterocyclyl radical is substituted with one or more radicals independently selected from the group consisting of halogen; -CN; -NO₂; oxo; alkyl; polyalkyl; haloalkyl; hydroxyalkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; -OR¹³; -NR¹³R¹⁴; -SR¹³; -S(O)R¹³; -SO₂R¹³; -SO₃R¹³; -NR¹³OR¹⁴; -NR¹³NR¹⁴R¹⁵; -CO₂R¹³; -OM; -SO₂OM; -SO₂NR¹³R¹⁴; -C(O)NR¹³R¹⁴; -C(O)OM; -COR¹³; -NR¹³C(O)R¹⁴; -NR¹³C(O)NR¹⁴R¹⁵; -NR¹³CO₂R¹⁴; -OC(O)R¹³; -OC(O)NR¹³R¹⁴; -NR¹³SOR¹⁴; -NR¹³SO₂R¹⁴; -NR¹³SONR¹⁴R¹⁵; -NR¹³SO₂NR¹⁴R¹⁵; -PR¹³R¹⁴; -P(O)R¹³R¹⁴; -P⁺R¹³R¹⁴R¹⁵A⁻; -P(OR¹³)OR¹⁴; -S⁺R¹³R¹⁴A⁻; and -N⁺R¹³R¹⁴R¹⁵A⁻; and

[167] wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether substituents of the R^3 radical optionally may be further substituted with one or more radicals selected from the group consisting of -CN; halogen; hydroxy; oxo; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclyl; -OR⁷; -NR⁷R⁸; -SR⁷; -S(O)R⁷; -SO₂R⁷; -SO₃R⁷; -CO₂R⁷; -CONR⁷R⁸; -N⁺R⁷R⁸R⁹A⁻; -P(O)R⁷R⁸; -PR⁷R⁸; -P⁺R⁷R⁸R⁹A⁻; and -P(O)(OR⁷)OR⁸; and

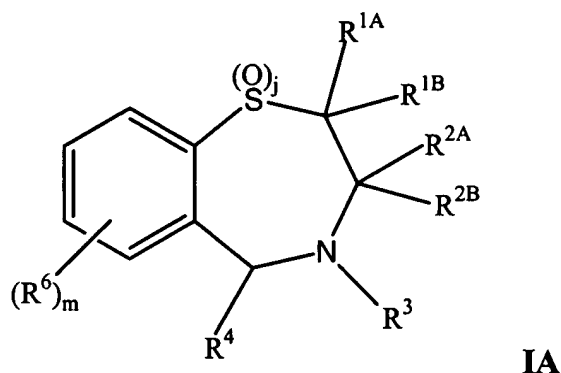
[168] wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether substituents of the R^3 radical optionally may have one or more carbons replaced by

-O-; -NR⁷-; -N⁺R⁷R⁸A⁻; -S-; -SO-; -SO₂-; -S⁺R⁷A⁻; -PR⁷-; -P(O)R⁷-; -P⁺R⁷R⁸A⁻; or phenylene; and

- [169] wherein R^7 and R^8 are independently selected from the group consisting of hydrogen; and alkyl; and
- [170] wherein R^9 , R^{10} , and R^w are independently selected from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; alkylammoniumalkyl; arylalkyl; heterocyclalkyl; carboxyalkyl; alkoxyalkyl; carboalkoxyalkyl; carboxyaryl; carboxyheterocyclyl; amino; alkylamino; carboxyalkylamino; alkoxyalkylamino; and acyl; and
- [171] wherein R^{11} and R^{12} are independently selected from the group consisting of hydrogen; -CN; halogen; oxo; alkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclalkyl; carboxyalkyl; alkoxyalkyl; carboalkoxyalkyl; cycloalkyl; cycloalkenyl; haloalkyl; hydroxyalkyl; cyanoalkyl; $-OR^9$; $-NR^9R^{10}$; $-SR^9$; $-S(O)R^9$; $-SO_2R^9$; $-SO_3R^9$; $-CO_2R^9$; and $-CONR^9R^{10}$; or
- [172] R^{11} and R^{12} together with the carbon atom to which they are attached form a cyclic ring; and
- [173] wherein R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclalkyl; quaternary heterocyclalkyl; alkylarylalkyl; alkylheterocyclalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether; or
- [174] wherein R^{13} and R^{14} together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocyclyl that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy, and quaternary salts; or
- [175] wherein R^{14} and R^{15} together with the nitrogen atom to which they are attached form a cyclic ring; and

- [176] wherein the R^{13} , R^{14} , and R^{15} alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclalkyl; quaternary heterocyclalkyl; alkylarylalkyl; alkylheterocyclalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may be substituted with one or more radicals selected from the group consisting of halogen; -CN; sulfo; oxo; alkyl; haloalkyl; hydroxyalkyl; sulfoalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; quaternary heterocyclalkyl; carboxy; carboxyalkyl; guanidiny; $-OR^{16}$; $-NR^9R^{10}$; $-N^+R^9R^{10}R^wA^-$; $-SR^{16}$; $-S(O)R^9$; $-SO_2R^9$; $-SO_3R^{16}$; $-CO_2R^{16}$; $-CONR^9R^{10}$; $-SO_2NR^9R^{10}$; $-PO(OR^{16})OR^{17}$; $-P^9R^{10}$; $-P^+R^9R^{10}R^{11}A^-$; $-S^+R^9R^{10}A^-$; and carbohydrate residue; and
- [177] wherein the R^{13} , R^{14} , and R^{15} alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclalkyl; quaternary heterocyclalkyl; alkylarylalkyl; alkylheterocyclalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may have one or more carbons replaced by -O-; $-NR^9$; $-N^+R^9R^{10}A^-$; -S-; -SO-; $-SO_2$; $-S^+R^9A^-$; $-PR^9$; $-P^+R^9R^{10}A^-$; $-P(O)R^9$; phenylene; carbohydrate residue; amino acid residue; peptide residue; or polypeptide residue; and
- [178] wherein R^{16} and R^{17} are independently selected from the group consisting of R^9 and M; and
- [179] wherein A is a pharmaceutically acceptable cation and M is a pharmaceutically acceptable cation; and
- [180] R^4 is R^5 .

[181] Within the compounds of Formula I is a class of compounds of specific interest corresponding to Formula IA:



[182] wherein: $j = 1$ or 2 ;

[183] R^{1A} and R^{1B} are independently selected from hydrogen and alkyl; and

[184] R^{2A} and R^{2B} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, and aralkyl; or

[185] R^{2A} and R^{2B} together with the carbon atom to which they are attached form a C_{3-7} cycloalkyl group; and

[186] independently selected from the group consisting of hydrogen, oxo, acyl, thioacyl, and R^5 ; and

[187] j , m , R^3 , R^4 and R^6 are as previously defined above for the compounds of Formula I;

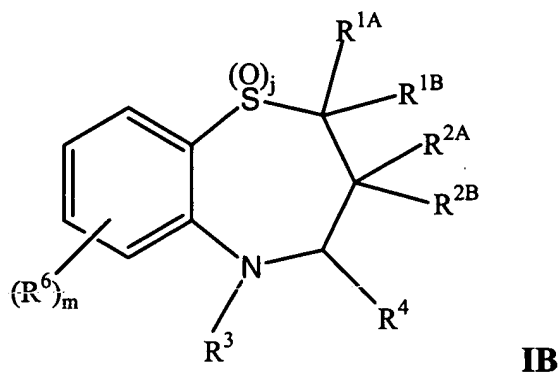
[188] provided that at least one of R^3 , R^4 and R^6 is R^5 ; and

[189] provided that the R^5 alkyl, cycloalkyl, aryl, heterocyclyl, and $-OR^9$ radicals are not substituted with $-O(CH_2)_{1-4}NR'R''R'''$ wherein R' , R'' and R''' are independently selected from hydrogen and alkyl; and

[190] provided that at least one of the following conditions is satisfied:

[191] (a) the R^5 moiety possesses an overall positive charge; and/or

- [192] (b) the R^5 moiety comprises a quaternary ammonium group or a quaternary amine salt; and/or
- [193] (c) the R^5 moiety comprises at least two carboxy groups.
- [194] Within the compounds of Formula I is another class of compounds of specific interest corresponding to Formula IB:



- [195] wherein: $j = 1$ or 2 ;
- [196] R^{1A} and R^{1B} are independently selected from hydrogen and alkyl; and
- [197] R^{2A} and R^{2B} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, and aralkyl; or
- [198] R^{2A} and R^{2B} together with the carbon atom to which they are attached form a C_{3-7} cycloalkyl group; and
- [199] independently selected from the group consisting of hydrogen, oxo, acyl, thioacyl, and R^5 ; and
- [200] j , m , R^3 , R^4 and R^6 are as previously defined above for the compounds of Formula I;
- [201] provided that at least one of R^3 , R^4 and R^6 is R^5 ; and

[202] provided that the R^5 alkyl, cycloalkyl, aryl, heterocyclyl, and $-OR^9$ radicals are not substituted with $-O(CH_2)_{1-4}NR'R''R'''$ wherein R' , R'' and R''' are independently selected from hydrogen and alkyl; and

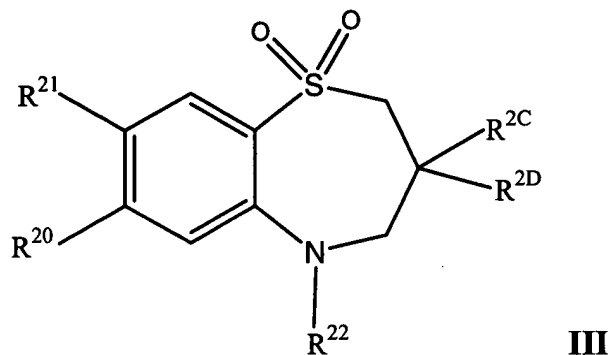
[203] provided that at least one of the following conditions is satisfied:

[204] (a) the R^5 moiety possesses an overall positive charge; and/or

[205] (b) the R^5 moiety comprises a quaternary ammonium group or a quaternary amine salt; and/or

[206] (c) the R^5 moiety comprises at least two carboxy groups.

[207] Within the compounds of Formula I is a class of compounds of particular interest corresponding to Formula III:



[208] wherein:

[209] R^{2C} and R^{2D} are independently selected from C_{1-6} alkyl; and

[210] R^{20} is selected from the group consisting of halogen and R^{23} ;

[211] R^{21} is selected from the group consisting of hydroxy, alkoxy, and R^{23} ; and

[212] wherein R^{23} is aryl substituted with one or more radicals independently selected from the group consisting of halogen; $-CN$; $-NO_2$; oxo; alkyl; polyalkyl; haloalkyl; hydroxyalkyl; cycloalkyl; alkenyl; alkynyl; aryl;

heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; polyether;
-OR¹³; -NR¹³R¹⁴; -SR¹³;

-S(O)R¹³; -SO₂R¹³; -SO₃R¹³; -NR¹³OR¹⁴; -NR¹³NR¹⁴R¹⁵; -CO₂R¹³; -
OM; -SO₂OM; -SO₂NR¹³R¹⁴; -C(O)NR¹³R¹⁴; -C(O)OM; -COR¹³; -
NR¹³C(O)R¹⁴;

-NR¹³C(O)NR¹⁴R¹⁵; -NR¹³CO₂R¹⁴; -OC(O)R¹³; -OC(O)NR¹³R¹⁴; -NR¹³SOR¹⁴;

-NR¹³SO₂R¹⁴; -NR¹³SONR¹⁴R¹⁵; -NR¹³SO₂NR¹⁴R¹⁵; -PR¹³R¹⁴; -P(O)R¹³R¹⁴;

-P⁺R¹³R¹⁴R¹⁵A⁻; -P(OR¹³)OR¹⁴; -S⁺R¹³R¹⁴A⁻; and -N⁺R¹³R¹⁴R¹⁵A⁻;
and

[213] wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether substituents of the R²³ aryl optionally may be further substituted with one or more radicals selected from the group consisting of -CN; halogen; hydroxy; oxo; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclyl; -OR⁷; -NR⁷R⁸; -SR⁷; -S(O)R⁷; -SO₂R⁷; -SO₃R⁷; -CO₂R⁷; -CONR⁷R⁸; -N⁺R⁷R⁸R⁹A⁻; -P(O)R⁷R⁸; -PR⁷R⁸; -P⁺R⁷R⁸R⁹A⁻; and -P(O)(OR⁷)OR⁸; and

[214] wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether substituents of the R²³ aryl optionally may have one or more carbons replaced by -O-; -NR⁷-; -N⁺R⁷R⁸A⁻; -S-; -SO-; -SO₂-; -S⁺R⁷A⁻; -PR⁷-; -P(O)R⁷-; -P⁺R⁷R⁸A⁻; or phenylene; and

[215] wherein R⁷ and R⁸ are independently selected from the group consisting of hydrogen; and alkyl; and

- [216] wherein R^9 , R^{10} , and R^W are independently selected from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; alkylammoniumalkyl; arylalkyl; heterocyclalkyl; carboxyalkyl; alkoxyalkyl; carboalkoxyalkyl; carboxyaryl; carboxyheterocyclyl; amino; alkylamino; carboxyalkylamino; alkoxyalkylamino; and acyl; and
- [217] wherein R^{11} and R^{12} are independently selected from the group consisting of hydrogen; -CN; halogen; oxo; alkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclalkyl; carboxyalkyl; alkoxyalkyl; carboalkoxyalkyl; cycloalkyl; cycloalkenyl; haloalkyl; hydroxyalkyl; cyanoalkyl; $-OR^9$; $-NR^9R^{10}$; $-SR^9$; $-S(O)R^9$; $-SO_2R^9$; $-SO_3R^9$; $-CO_2R^9$; and $-CONR^9R^{10}$; or
- [218] R^{11} and R^{12} together with the carbon atom to which they are attached form a cyclic ring; and
- [219] wherein R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclalkyl; quaternary heterocyclalkyl; alkylarylalkyl; alkylheterocyclalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether; or
- [220] wherein R^{13} and R^{14} together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocyclyl that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy, and quaternary salts; or
- [221] wherein R^{14} and R^{15} together with the nitrogen atom to which they are attached form a cyclic ring; and
- [222] wherein the R^{13} , R^{14} , and R^{15} alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl;

heterocyclalkyl; quaternary heterocyclalkyl; alkylalkyl;
 alkylheterocyclalkyl; alkylammoniumalkyl; aminoalkyl;
 aminocarbonylalkyl; alkylaminocarbonylalkyl;
 carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may be
 substituted with one or more radicals selected from the group consisting of
 halogen; -CN; sulfo; oxo; alkyl; haloalkyl; hydroxyalkyl; sulfoalkyl; alkenyl;
 alkynyl; aryl; heterocycl; quaternary heterocycl; quaternary
 heterocyclalkyl; carboxy; carboxyalkyl; guanidiny; -OR¹⁶; -NR⁹R¹⁰; -N⁺
 R⁹R¹⁰R^wA⁻; -SR¹⁶; -S(O)R⁹; -SO₂R⁹; -SO₃R¹⁶; -CO₂R¹⁶; -CONR⁹R¹⁰; -
 SO₂NR⁹R¹⁰; -PO(OR¹⁶)OR¹⁷; -P⁹R¹⁰; -P⁺R⁹R¹⁰R¹¹A⁻; -S⁺R⁹R¹⁰A⁻;
 and carbohydrate residue; and

[223] wherein the R¹³, R¹⁴, and R¹⁵ alkyl; haloalkyl; cycloalkyl; polyalkyl;
 alkenyl; alkynyl; aryl; heterocycl; quaternary heterocycl; arylalkyl;
 heterocyclalkyl; quaternary heterocyclalkyl; alkylalkyl;
 alkylheterocyclalkyl; alkylammoniumalkyl; aminoalkyl;
 aminocarbonylalkyl; alkylaminocarbonylalkyl;
 carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may have
 one or more carbons replaced by -O-; -NR⁹-; -N⁺R⁹R¹⁰A⁻; -S-; -SO-; -SO₂-;
 -S⁺R⁹A⁻; -PR⁹-; -P⁺R⁹R¹⁰A⁻; -P(O)R⁹-; phenylene; carbohydrate residue;
 amino acid residue; peptide residue; or polypeptide residue; and

[224] wherein R¹⁶ and R¹⁷ are independently selected from the group consisting of
 R⁹ and M; and

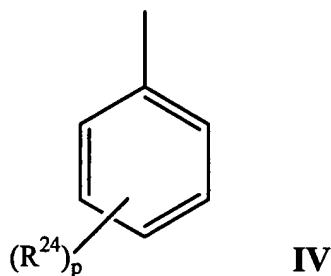
[225] wherein A⁻ is a pharmaceutically acceptable anion and M is a
 pharmaceutically acceptable cation; and

[226] R²² is unsubstituted phenyl or R²³; or

[227] a pharmaceutically acceptable salt, solvate, or prodrug thereof;

[228] provided that at least one of R²⁰, R²¹ and R²² is R²³.

[229] Preferably, R^{23} is:



[230] wherein

[231] p is 0, 1, 2, 3 or 4; and

[232] one or more R^{24} are independently selected from the group consisting of halogen; -CN; -NO₂; oxo; alkyl; polyalkyl; haloalkyl; hydroxyalkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; -OR¹³; -NR¹³R¹⁴; -SR¹³; -S(O)R¹³; -SO₂R¹³; -SO₃R¹³; -NR¹³OR¹⁴; -NR¹³NR¹⁴R¹⁵; -CO₂R¹³; -OM; -SO₂OM; -SO₂NR¹³R¹⁴; -C(O)NR¹³R¹⁴; -C(O)OM; -COR¹³; -NR¹³C(O)R¹⁴; -NR¹³C(O)NR¹⁴R¹⁵; -NR¹³CO₂R¹⁴; -OC(O)R¹³; -OC(O)NR¹³R¹⁴; -NR¹³SOR¹⁴; -NR¹³SO₂R¹⁴; -NR¹³SONR¹⁴R¹⁵; -NR¹³SO₂NR¹⁴R¹⁵; -PR¹³R¹⁴; -P(O)R¹³R¹⁴; -P⁺R¹³R¹⁴R¹⁵A⁻; -P(OR¹³)OR¹⁴; -S⁺R¹³R¹⁴A⁻; and -N⁺R¹³R¹⁴R¹⁵A⁻; and

[233] wherein the R^{24} alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether radicals optionally may be further substituted with one or more radicals selected from the group consisting of -CN; halogen; hydroxy; oxo; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclyl; -OR⁷; -NR⁷R⁸; -SR⁷; -S(O)R⁷; -SO₂R⁷; -SO₃R⁷; -CO₂R⁷; -CONR⁷R⁸; -N⁺R⁷R⁸R⁹A⁻; -P(O)R⁷R⁸; -PR⁷R⁸; -P⁺R⁷R⁸R⁹A⁻; and -P(O)(OR⁷)OR⁸; and

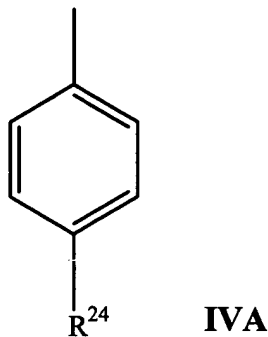
- [234] wherein the R^{24} alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclalkyl, and polyether radicals optionally may have one or more carbons replaced by -O-; $-NR^7$ -; $-N^+R^7R^8A^-$; -S-; -SO-; $-SO_2$ -; $-S^+R^7A^-$; $-PR^7$ -; $-P(O)R^7$ -; $-P^+R^7R^8A^-$; or phenylene; and
- [235] wherein R^7 and R^8 are independently selected from the group consisting of hydrogen; and alkyl; and
- [236] wherein R^9 , R^{10} , and R^w are independently selected from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; alkylammoniumalkyl; arylalkyl; heterocyclalkyl; carboxyalkyl; alkoxyalkyl; carboalkoxyalkyl; carboxyaryl; carboxyheterocyclyl; amino; alkylamino; carboxyalkylamino; alkoxyalkylamino; and acyl; and
- [237] wherein R^{11} and R^{12} are independently selected from the group consisting of hydrogen; -CN; halogen; oxo; alkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclalkyl; carboxyalkyl; alkoxyalkyl; carboalkoxyalkyl; cycloalkyl; cycloalkenyl; haloalkyl; hydroxyalkyl; cyanoalkyl; $-OR^9$; $-NR^9R^{10}$; $-SR^9$; $-S(O)R^9$; $-SO_2R^9$; $-SO_3R^9$; $-CO_2R^9$; and $-CONR^9R^{10}$; or
- [238] R^{11} and R^{12} together with the carbon atom to which they are attached form a cyclic ring; and
- [239] wherein R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclalkyl; quaternary heterocyclalkyl; alkylarylalkyl; alkylheterocyclalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether; or

- [240] wherein R^{13} and R^{14} together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocyclyl that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy, and quaternary salts; or
- [241] wherein R^{14} and R^{15} together with the nitrogen atom to which they are attached form a cyclic ring; and
- [242] wherein the R^{13} , R^{14} , and R^{15} alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may be substituted with one or more radicals selected from the group consisting of halogen; -CN; sulfo; oxo; alkyl; haloalkyl; hydroxyalkyl; sulfoalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; quaternary heterocyclylalkyl; carboxy; carboxyalkyl; guanidiny; $-OR^{16}$; $-NR^9R^{10}$; $-N^+R^9R^{10}R^wA^-$; $-SR^{16}$; $-S(O)R^9$; $-SO_2R^9$; $-SO_3R^{16}$; $-CO_2R^{16}$; $-CONR^9R^{10}$; $-SO_2NR^9R^{10}$; $-PO(OR^{16})OR^{17}$; $-P^9R^{10}$; $-P^+R^9R^{10}R^{11}A^-$; $-S^+R^9R^{10}A^-$; and carbohydrate residue; and
- [243] wherein the R^{13} , R^{14} , and R^{15} alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may have one or more carbons replaced by $-O-$; $-NR^9-$; $-N^+R^9R^{10}A^-$; $-S-$; $-SO-$; $-SO_2-$; $-S^+R^9A^-$; $-PR^9-$; $-P^+R^9R^{10}A^-$; $-P(O)R^9$; phenylene; carbohydrate residue; amino acid residue; peptide residue; or polypeptide residue; and

[244] wherein R^{16} and R^{17} are independently selected from the group consisting of R^9 and M; and

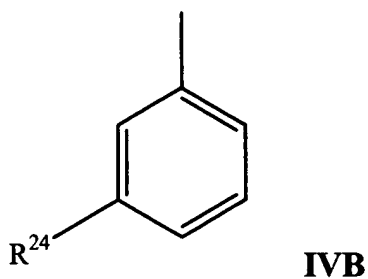
[245] wherein A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation.

[246] In one embodiment, R^{23} is:



[247] wherein R^{24} is as defined above.

[248] In another embodiment, R^{23} is:



[249] wherein R^{24} is as defined above.

[250] In another embodiment:

[251] R^{24} is independently selected from the group consisting of $-OR^{13}$, $-NR^{13}R^{14}$, $-NR^{13}C(O)R^{14}$, $-OC(O)NR^{13}R^{14}$, and $-NR^{13}SO_2R^{14}$, and

[252] wherein R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of alkyl, polyether, aryl, quaternary heterocycle, arylalkyl, heterocyclalkyl, quaternary heterocyclalkyl, alkylheterocyclalkyl, and alkylammoniumalkyl,

[253] wherein alkyl optionally has one or more carbons replaced by O or $N^+R^9R^{10}A^-$, and

[254] wherein R^{13} , R^{14} , and R^{15} are optionally substituted with one or more groups selected from the group consisting of hydroxy, carboxy, alkyl, quaternary heterocyclalkyl, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$, $-S(O)_3R^9$, $-NR^9R^{10}$, $-N^+R^9R^{11}R^{12}A^-$, $-CONR^9R^{10}$, and $-PO(OR^{16})OR^{17}$, and

[255] wherein R^9 and R^{10} are independently selected from the group consisting of hydrogen, alkyl, heterocyclalkyl, carboxyalkyl, carboalkoxyalkyl, and carboxyalkylheterocycle; and

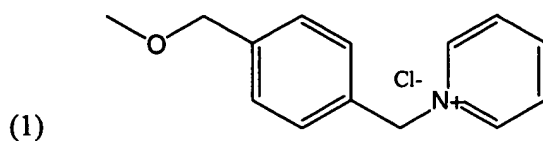
[256] wherein R^{11} and R^{12} are independently alkyl; and

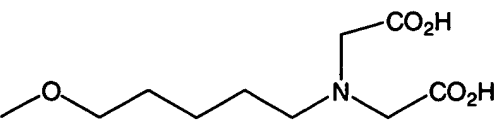
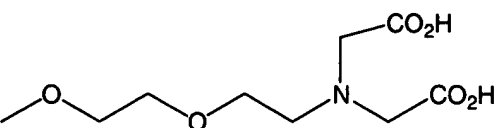
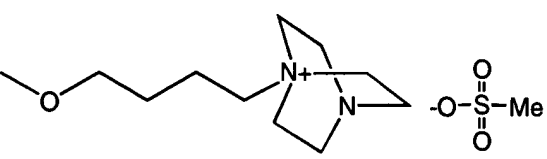
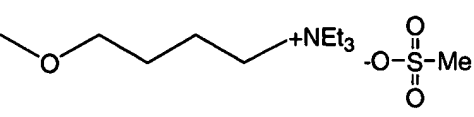
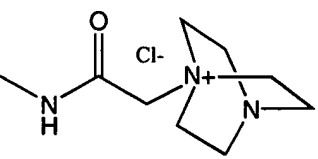
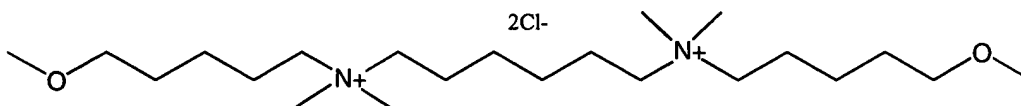
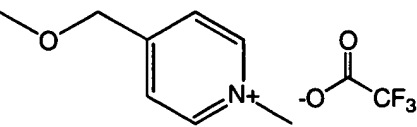
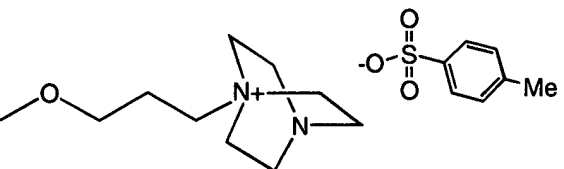
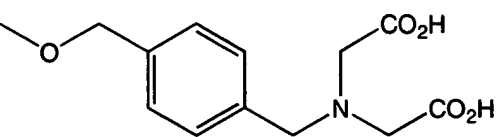
[257] wherein A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation.

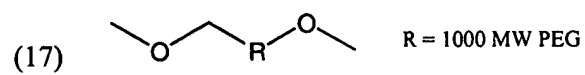
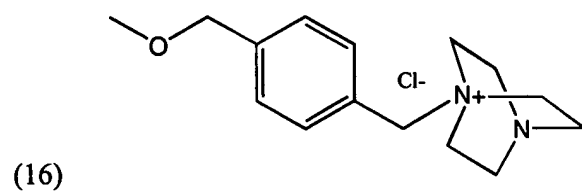
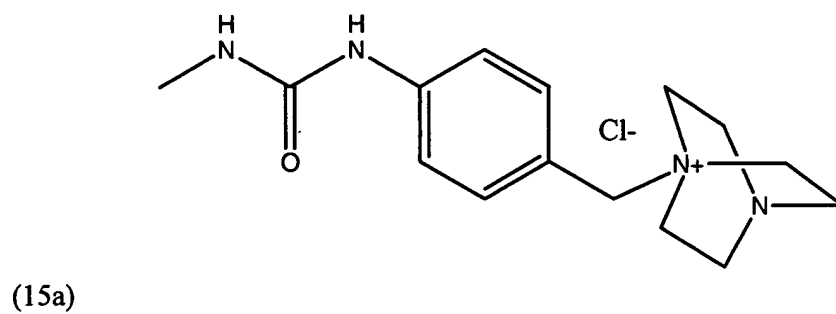
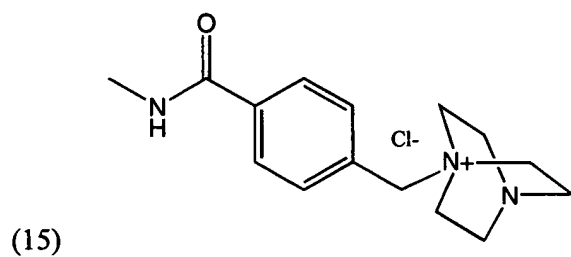
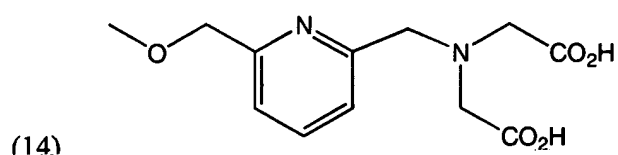
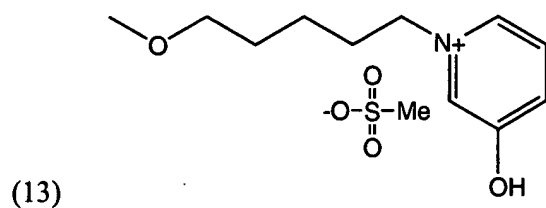
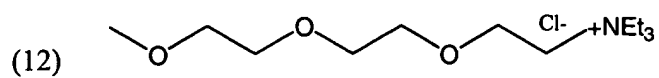
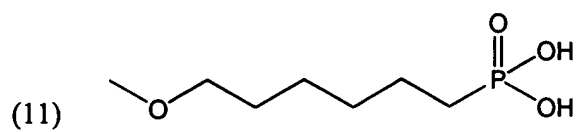
[258] In another embodiment, R^{24} is selected from the group consisting of:

TABLE 2

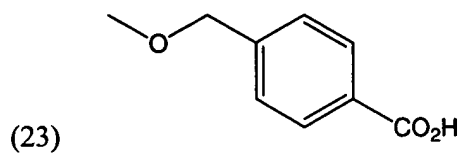
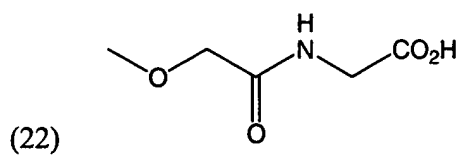
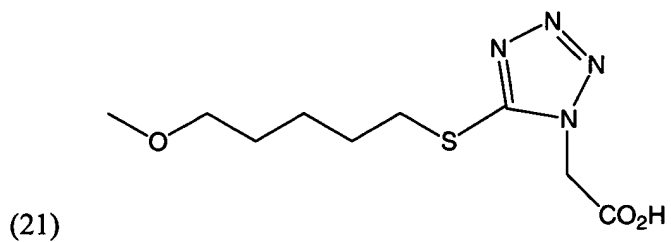
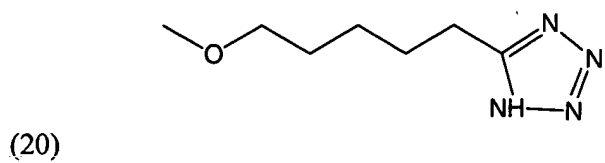
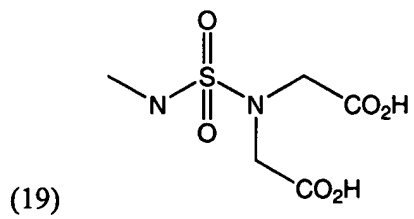
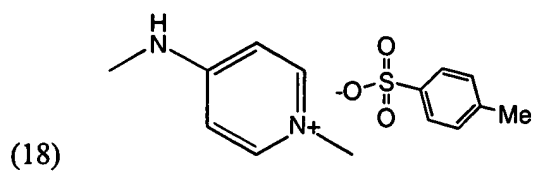
R^{24}

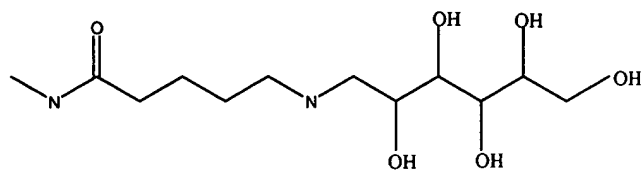
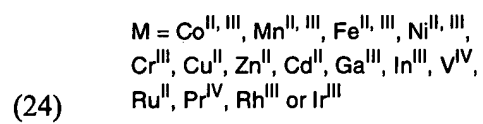
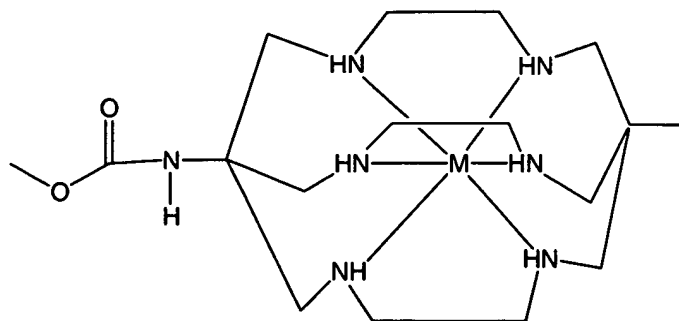


- (2) 
- (3) 
- (4) 
- (5) 
- (6) 
- (7) 
- (8) 
- (9) 
- (10) 

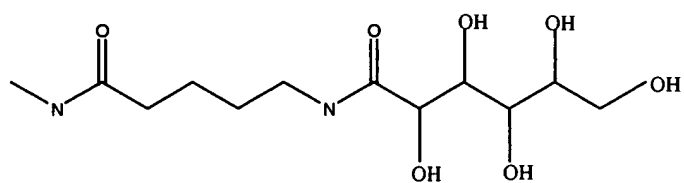


R = 1000 MW PEG

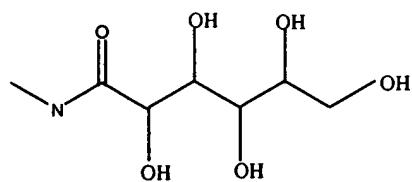




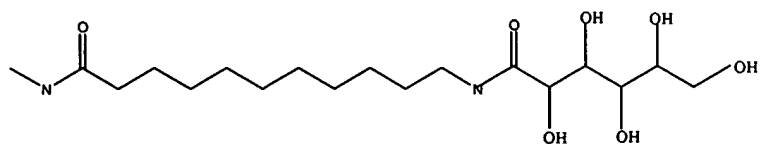
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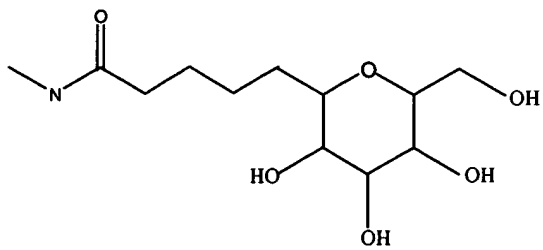
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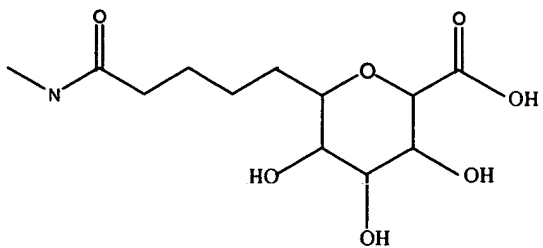
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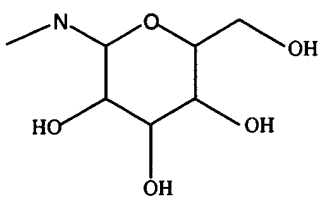
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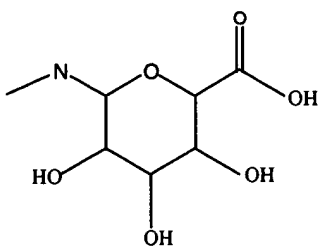
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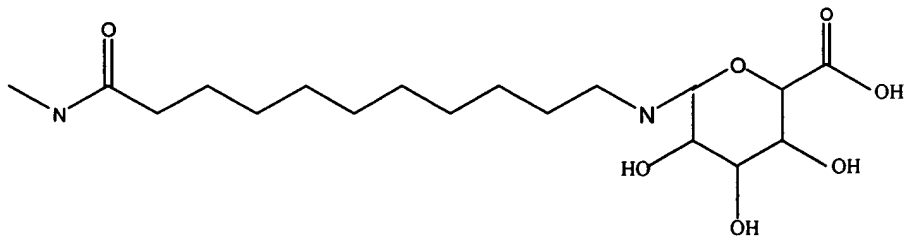
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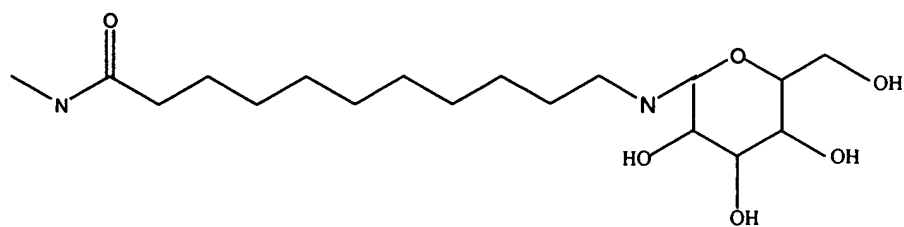
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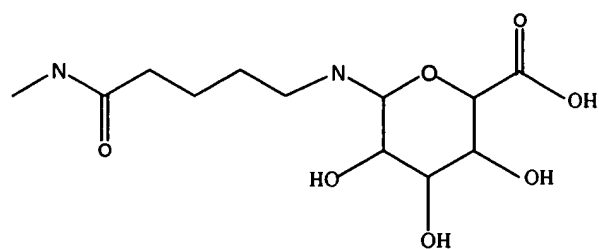
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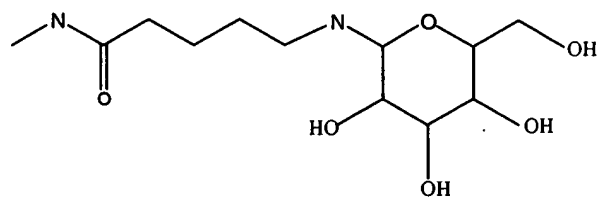
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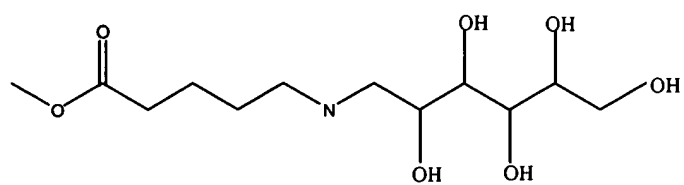
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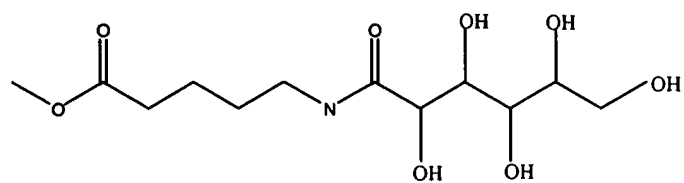
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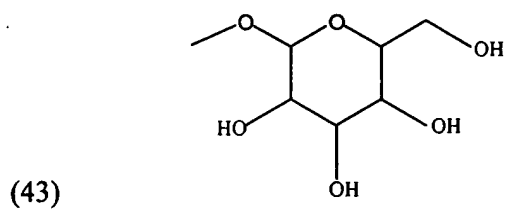
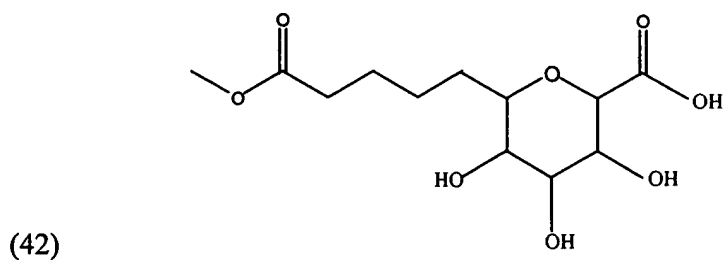
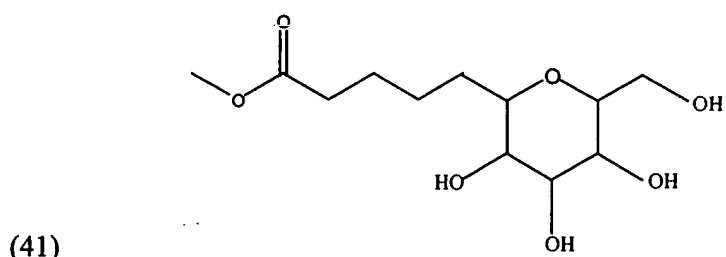
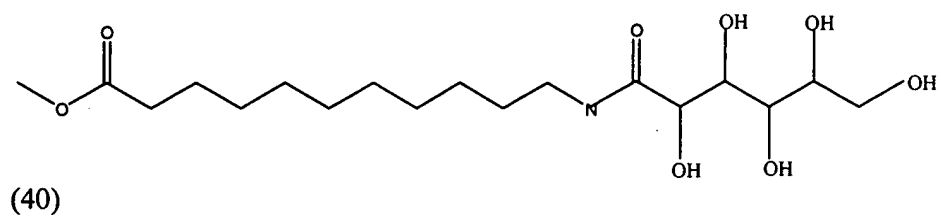
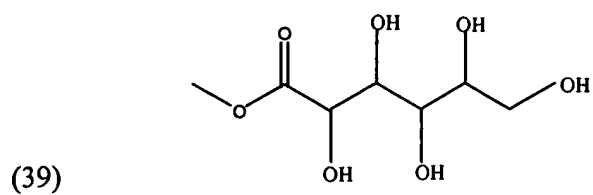
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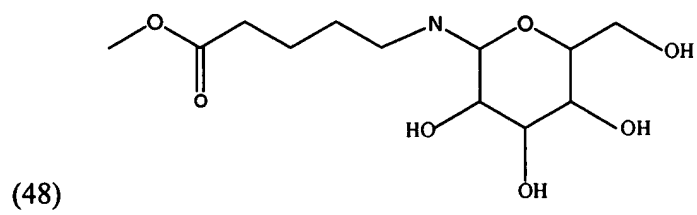
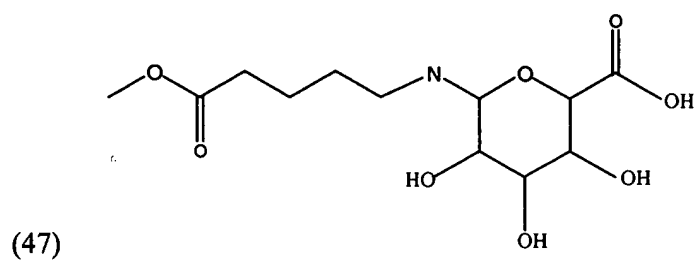
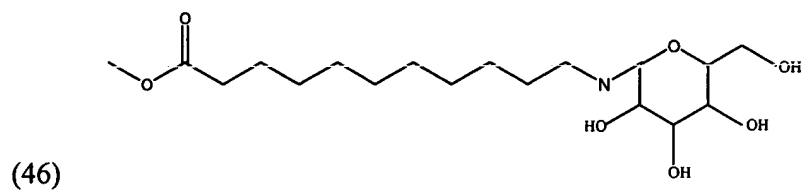
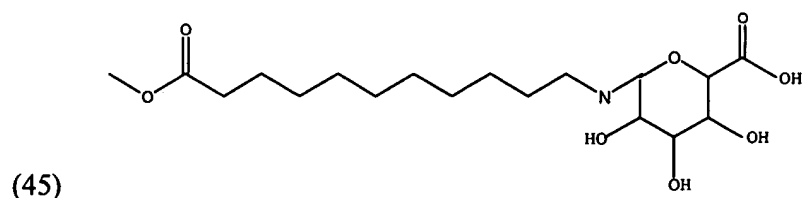
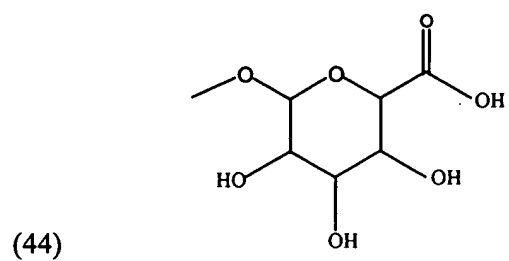


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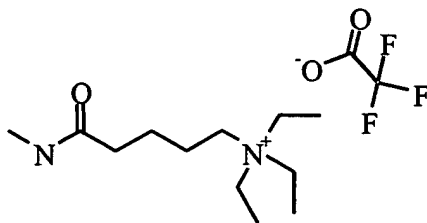


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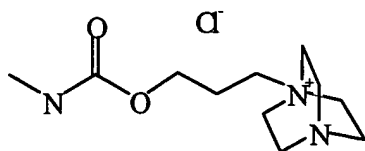




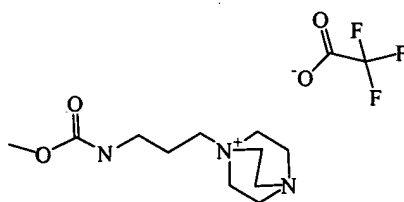
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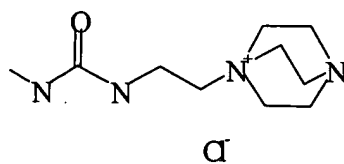
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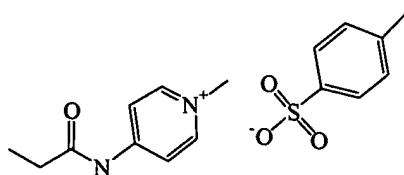
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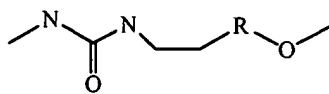
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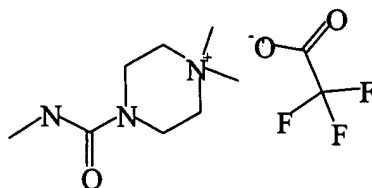
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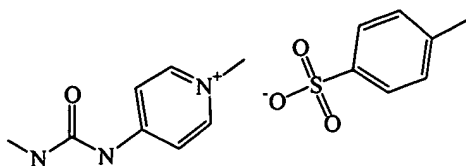
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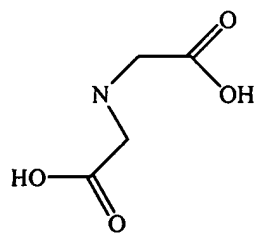
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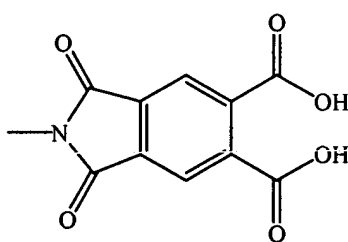
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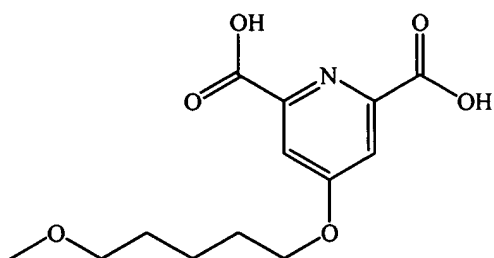
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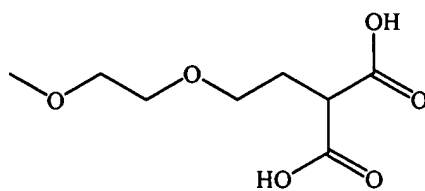
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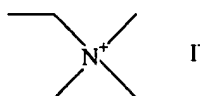
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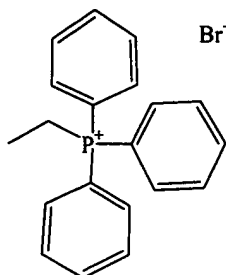
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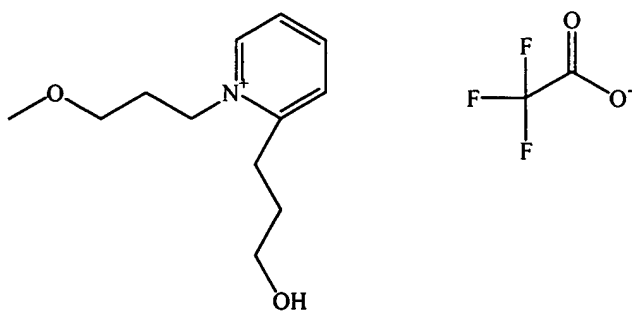
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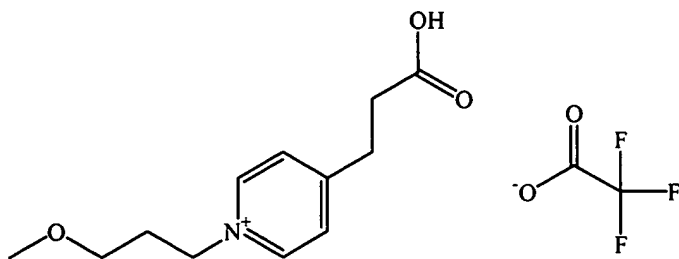
(63)



(64)



(65)



0 **1** **2** **3** **4** **5** **6** **7** **8** **9**



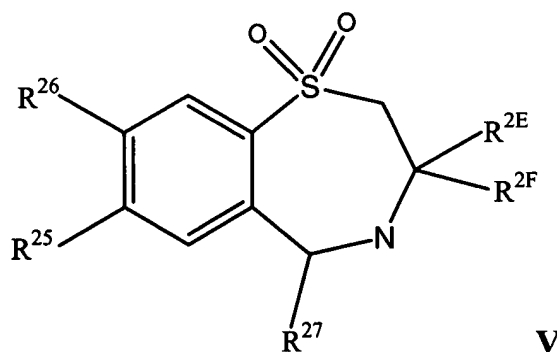
[259] Optionally, R^{24} may be selected from the following: (1) – (24), (25) – (48) or (49) – (70) from Table 2. Further, R^{24} may be acidic or contain a quaternary ammonium nitrogen. Even further, R^{24} may be selected from the following: (1) – (5), (6) – (10), (11) – (15), (16) – (20), (21) – (25), (26) – (30), (31) – (35), (36) – (40), (41) – (45), (46) – (50), (51) – (55), (56) – (60), (61) – (65), (66) – (70), or combinations thereof.

[260] In another embodiment of the compounds of Formula III, R^{20} is chloro, and R^{21} is selected from the group consisting of hydroxy and methoxy.

[261] In another embodiment of the compounds of Formula III, one of R^{2C} and R^{2D} is ethyl and the other of R^{2C} and R^{2D} is n-butyl; R^{20} is chloro; and R^{21} is hydroxy.

[262] In another embodiment of the compounds of Formula III, one of R^{2C} and R^{2D} is ethyl and the other of R^{2C} and R^{2D} is n-butyl; R^{20} is chloro; and R^{21} is methoxy.

[263] Within the compounds of Formula I is another class of compounds of particular interest corresponding to Formula V:



[264] wherein:

[265] R^{2E} and R^{2F} are independently selected from C_{1-6} alkyl; and

- [266] R^{25} and R^{26} are independently selected from the group consisting of hydrogen, alkoxy, and R^{28} ;
- [267] wherein R^{28} is aryl substituted with one or more radicals independently selected from the group consisting of halogen; -CN; -NO₂; oxo; alkyl; polyalkyl; haloalkyl; hydroxyalkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclalkyl; polyether; -OR¹³; -NR¹³R¹⁴; -SR¹³; -S(O)R¹³; -SO₂R¹³; -SO₃R¹³; -NR¹³OR¹⁴; -NR¹³NR¹⁴R¹⁵; -CO₂R¹³; -OM; -SO₂OM; -SO₂NR¹³R¹⁴; -C(O)NR¹³R¹⁴; -C(O)OM; -COR¹³; -NR¹³C(O)R¹⁴; -NR¹³C(O)NR¹⁴R¹⁵; -NR¹³CO₂R¹⁴; -OC(O)R¹³; -OC(O)NR¹³R¹⁴; -NR¹³SOR¹⁴; -NR¹³SO₂R¹⁴; -NR¹³SONR¹⁴R¹⁵; -NR¹³SO₂NR¹⁴R¹⁵; -PR¹³R¹⁴; -P(O)R¹³R¹⁴; -P⁺R¹³R¹⁴R¹⁵A⁻; -P(OR¹³)OR¹⁴; -S⁺R¹³R¹⁴A⁻; and -N⁺R¹³R¹⁴R¹⁵A⁻; and
- [268] wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclalkyl, and polyether substituents of the R^{28} aryl optionally may be further substituted with one or more radicals selected from the group consisting of -CN; halogen; hydroxy; oxo; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclalkyl; quaternary heterocyclyl; -OR⁷; -NR⁷R⁸; -SR⁷; -S(O)R⁷; -SO₂R⁷; -SO₃R⁷; -CO₂R⁷; -CONR⁷R⁸; -N⁺R⁷R⁸R⁹A⁻; -P(O)R⁷R⁸; -PR⁷R⁸; -P⁺R⁷R⁸R⁹A⁻; and -P(O)(OR⁷)OR⁸; and
- [269] wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclalkyl, and polyether substituents of the R^{28} aryl optionally may have one or more carbons replaced by -O-; -NR⁷-; -N⁺R⁷R⁸A⁻; -S-;

-SO-; -SO₂-; -S⁺R⁷A⁻; -PR⁷-; -P(O)R⁷-; -P⁺R⁷R⁸A⁻; or phenylene;
and

[270] wherein R⁷ and R⁸ are independently selected from the group consisting of hydrogen; and alkyl; and

[271] wherein R⁹, R¹⁰, and R^w are independently selected from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; alkylammoniumalkyl; arylalkyl; heterocyclalkyl; carboxyalkyl; alkoxyalkyl; carboalkoxyalkyl; carboxyaryl; carboxyheterocyclyl; amino; alkylamino; carboxyalkylamino; alkoxyalkylamino; and acyl; and

[272] wherein R¹¹ and R¹² are independently selected from the group consisting of hydrogen; -CN; halogen; oxo; alkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclalkyl; carboxyalkyl; alkoxyalkyl; carboalkoxyalkyl; cycloalkyl; cycloalkenyl; haloalkyl; hydroxyalkyl; cyanoalkyl; -OR⁹; -NR⁹R¹⁰; -SR⁹; -S(O)R⁹; -SO₂R⁹; -SO₃R⁹; -CO₂R⁹; and -CONR⁹R¹⁰; or

[273] R¹¹ and R¹² together with the carbon atom to which they are attached form a cyclic ring; and

[274] wherein R¹³, R¹⁴, and R¹⁵ are independently selected from the group consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclalkyl; quaternary heterocyclalkyl; alkylarylalkyl; alkylheterocyclalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether; or

[275] wherein R¹³ and R¹⁴ together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocyclyl that is optionally

substituted with one or more radicals selected from the group consisting of oxo, carboxy, and quaternary salts; or

- [276] wherein R^{14} and R^{15} together with the nitrogen atom to which they are attached form a cyclic ring; and
- [277] wherein the R^{13} , R^{14} , and R^{15} alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclalkyl; quaternary heterocyclalkyl; alkylarylalkyl; alkylheterocyclalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may be substituted with one or more radicals selected from the group consisting of halogen; -CN; sulfo; oxo; alkyl; haloalkyl; hydroxyalkyl; sulfoalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; quaternary heterocyclalkyl; carboxy; carboxyalkyl; guanidynyl; $-OR^{16}$; $-NR^9R^{10}$; $-N^+R^9R^{10}R^wA^-$; $-SR^{16}$; $-S(O)R^9$; $-SO_2R^9$; $-SO_3R^{16}$; $-CO_2R^{16}$; $-CONR^9R^{10}$; $-SO_2NR^9R^{10}$; $-PO(OR^{16})OR^{17}$; $-P^9R^{10}$; $-P^+R^9R^{10}R^{11}A^-$; $-S^+R^9R^{10}A^-$; and carbohydrate residue; and
- [278] wherein the R^{13} , R^{14} , and R^{15} alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclalkyl; quaternary heterocyclalkyl; alkylarylalkyl; alkylheterocyclalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may have one or more carbons replaced by -O-; $-NR^9$; $-N^+R^9R^{10}A^-$; -S-; -SO-; $-SO_2$; $-S^+R^9A^-$; $-PR^9$; $-P^+R^9R^{10}A^-$; $-P(O)R^9$; phenylene; carbohydrate residue; amino acid residue; peptide residue; or polypeptide residue; and

[279] wherein R^{16} and R^{17} are independently selected from the group consisting of R^9 and M; and

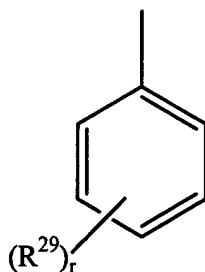
[280] wherein A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation; and

[281] R^{27} is unsubstituted phenyl or R^{28} ; or

[282] a pharmaceutically acceptable salt, solvate, or prodrug thereof;

[283] provided that at least one of R^{25} , R^{26} and R^{27} is R^{28} .

[284] Preferably, R^{28} is:



VI

[285] wherein

[286] r is 0, 1, 2, 3 or 4; and

[287] one or more R^{29} are independently selected from the group consisting of halogen; -CN; -NO₂; oxo; alkyl; polyalkyl; haloalkyl; hydroxyalkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; -OR¹³; -NR¹³R¹⁴; -SR¹³; -S(O)R¹³; -SO₂R¹³; -SO₃R¹³; -NR¹³OR¹⁴; -NR¹³NR¹⁴R¹⁵; -CO₂R¹³; -OM; -SO₂OM; -SO₂NR¹³R¹⁴; -C(O)NR¹³R¹⁴; -C(O)OM; -COR¹³; -NR¹³C(O)R¹⁴; -NR¹³C(O)NR¹⁴R¹⁵; -NR¹³CO₂R¹⁴; -OC(O)R¹³; -OC(O)NR¹³R¹⁴; -NR¹³SOR¹⁴; -NR¹³SO₂R¹⁴; -NR¹³SONR¹⁴R¹⁵; -NR¹³SO₂NR¹⁴R¹⁵; -PR¹³R¹⁴; -P(O)R¹³R¹⁴; -P⁺R¹³R¹⁴R¹⁵A⁻; -P(OR¹³)OR¹⁴; -S⁺R¹³R¹⁴A⁻; and -N⁺R¹³R¹⁴R¹⁵A⁻; and

- [288] wherein the R^{29} alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether radicals optionally may be further substituted with one or more radicals selected from the group consisting of -CN; halogen; hydroxy; oxo; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclyl; $-OR^7$; $-NR^7R^8$; $-SR^7$; $-S(O)R^7$; $-SO_2R^7$; $-SO_3R^7$; $-CO_2R^7$; $-CONR^7R^8$; $-N^+R^7R^8R^9A^-$; $-P(O)R^7R^8$; $-PR^7R^8$; $-P^+R^7R^8R^9A^-$; and $-P(O)(OR^7)OR^8$; and
- [289] wherein the R^{29} alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether radicals optionally may have one or more carbons replaced by -O-; $-NR^7$ -; $-N^+R^7R^8A^-$; -S-; -SO-; $-SO_2$ -; $-S^+R^7A^-$; $-PR^7$ -; $-P(O)R^7$ -; $-P^+R^7R^8A^-$; or phenylene; and
- [290] wherein R^7 and R^8 are independently selected from the group consisting of hydrogen; and alkyl; and
- [291] wherein R^9 , R^{10} , and R^W are independently selected from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; alkylammoniumalkyl; arylalkyl; heterocyclylalkyl; carboxyalkyl; alkoxyalkyl; carboalkoxyalkyl; carboxyaryl; carboxyheterocyclyl; amino; alkylamino; carboxyalkylamino; alkoxyalkylamino; and acyl; and
- [292] wherein R^{11} and R^{12} are independently selected from the group consisting of hydrogen; -CN; halogen; oxo; alkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; carboxyalkyl; alkoxyalkyl; carboalkoxyalkyl; cycloalkyl; cycloalkenyl; haloalkyl; hydroxyalkyl;

cyanoalkyl; -OR⁹; -NR⁹R¹⁰; -SR⁹; -S(O)R⁹; -SO₂R⁹; -SO₃R⁹; -CO₂R⁹; and -CONR⁹R¹⁰; or

- [293] R¹¹ and R¹² together with the carbon atom to which they are attached form a cyclic ring; and
- [294] wherein R¹³, R¹⁴, and R¹⁵ are independently selected from the group consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether; or
- [295] wherein R¹³ and R¹⁴ together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocyclyl that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy, and quaternary salts; or
- [296] wherein R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form a cyclic ring; and
- [297] wherein the R¹³, R¹⁴, and R¹⁵ alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may be substituted with one or more radicals selected from the group consisting of halogen; -CN; sulfo; oxo; alkyl; haloalkyl; hydroxyalkyl; sulfoalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; quaternary heterocyclylalkyl; carboxy; carboxyalkyl; guanidiny; -OR¹⁶;

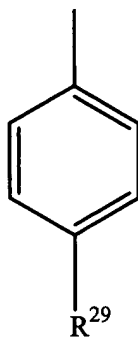
$-\text{NR}^9\text{R}^{10}$; $-\text{N}^+\text{R}^9\text{R}^{10}\text{R}^w\text{A}^-$; $-\text{SR}^{16}$; $-\text{S}(\text{O})\text{R}^9$; $-\text{SO}_2\text{R}^9$; $-\text{SO}_3\text{R}^{16}$; $-\text{CO}_2\text{R}^{16}$; $-\text{CONR}^9\text{R}^{10}$; $-\text{SO}_2\text{NR}^9\text{R}^{10}$; $-\text{PO}(\text{OR}^{16})\text{OR}^{17}$; $-\text{P}^9\text{R}^{10}$; $-\text{P}^+\text{R}^9\text{R}^{10}\text{R}^{11}\text{A}^-$; $-\text{S}^+\text{R}^9\text{R}^{10}\text{A}^-$; and carbohydrate residue; and

[298] wherein the R^{13} , R^{14} , and R^{15} alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclalkyl; quaternary heterocyclalkyl; alkylarylalkyl; alkylheterocyclalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may have one or more carbons replaced by $-\text{O}-$; $-\text{NR}^9-$; $-\text{N}^+\text{R}^9\text{R}^{10}\text{A}^-$; $-\text{S}-$; $-\text{SO}-$; $-\text{SO}_2-$; $-\text{S}^+\text{R}^9\text{A}^-$; $-\text{PR}^9-$; $-\text{P}^+\text{R}^9\text{R}^{10}\text{A}^-$; $-\text{P}(\text{O})\text{R}^9-$; phenylene; carbohydrate residue; amino acid residue; peptide residue; or polypeptide residue; and

[299] wherein R^{16} and R^{17} are independently selected from the group consisting of R^9 and M ; and

[300] wherein A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation.

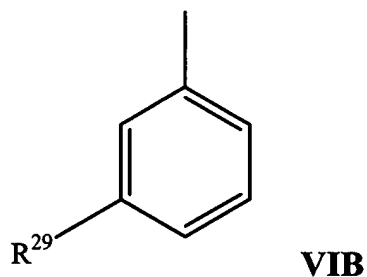
[301] In one embodiment, R^{28} is:



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[302] wherein R^{29} is as defined above.

[303] In another embodiment, R^{28} is:



[304] wherein R^{29} is as defined above.

[305] In another embodiment:

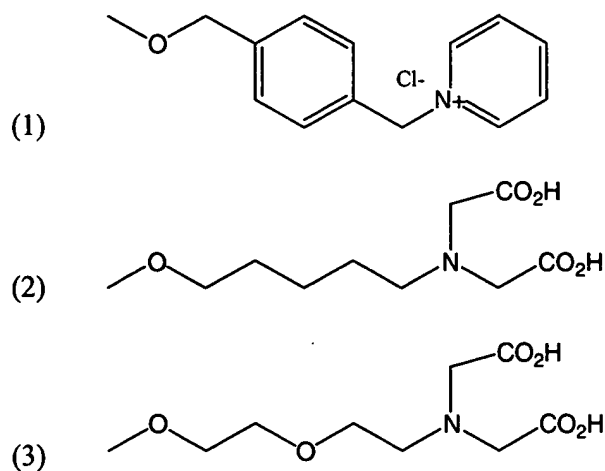
[306] R^{29} is independently selected from the group consisting of $-OR^{13}$, $-NR^{13}R^{14}$, $-NR^{13}C(O)R^{14}$, $-OC(O)NR^{13}R^{14}$, and $-NR^{13}SO_2R^{14}$, and

[307] wherein R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of alkyl, polyether, aryl, quaternary heterocycle, arylalkyl, heterocyclalkyl, quaternary heterocyclalkyl, alkylheterocyclalkyl, and alkylammoniumalkyl,

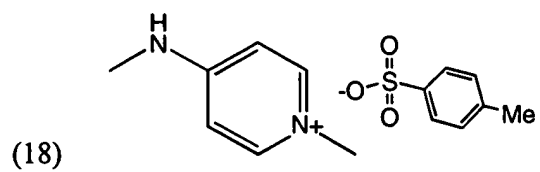
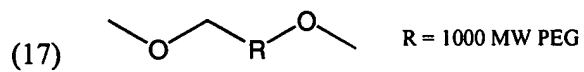
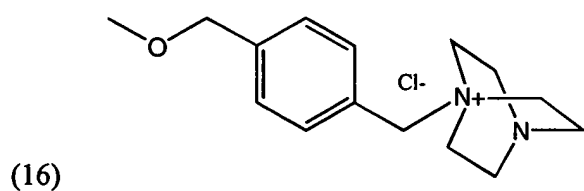
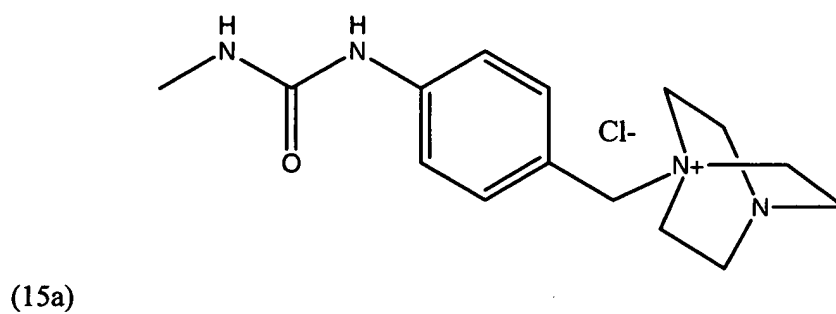
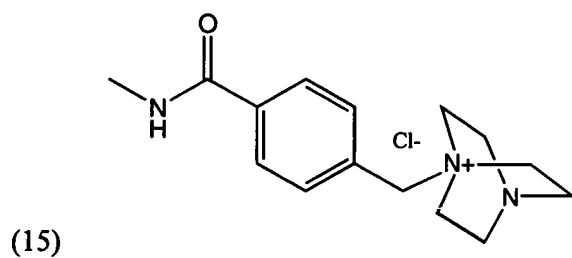
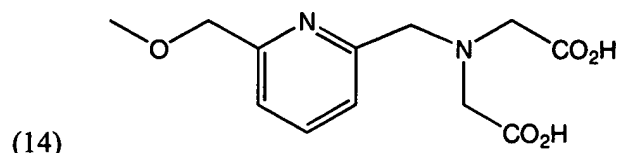
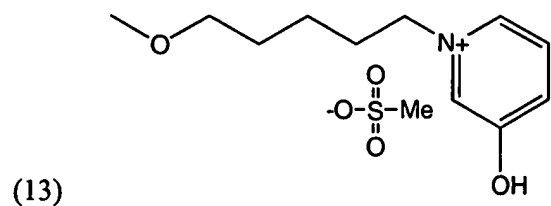
- [308] wherein alkyl optionally has one or more carbons replaced by O or $N^+R^9R^{10}A^-$, and
- [309] wherein R^{13} , R^{14} , and R^{15} are optionally substituted with one or more groups selected from the group consisting of hydroxy, carboxy, alkyl, quaternary heterocyclalkyl, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$, $-S(O)_3R^9$, $-NR^9R^{10}$, $-N^+R^9R^{11}R^{12}A^-$, $-CONR^9R^{10}$, and $-PO(OR^{16})OR^{17}$, and
- [310] wherein R^9 and R^{10} are independently selected from the group consisting of hydrogen, alkyl, heterocyclalkyl, carboxyalkyl, carboalkoxyalkyl, and carboxyalkylheterocycle; and
- [311] wherein R^{11} and R^{12} are independently alkyl; and
- [312] wherein A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation.
- [313] In another embodiment, R^{29} is selected from the group consisting of:

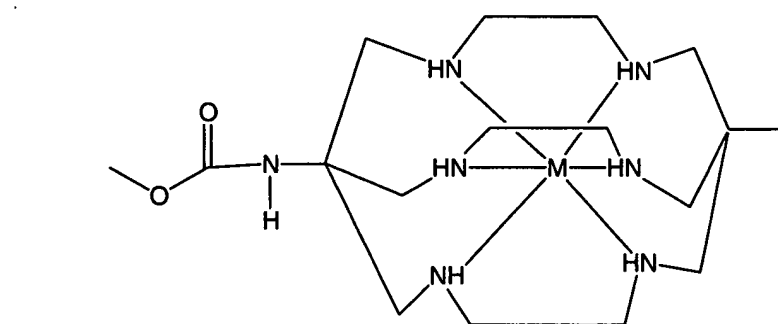
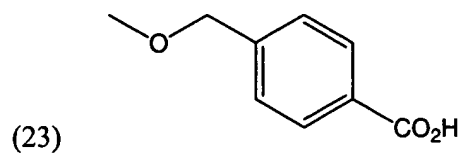
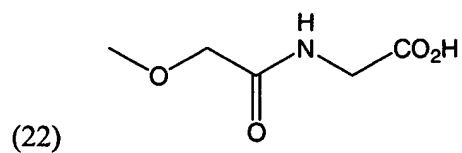
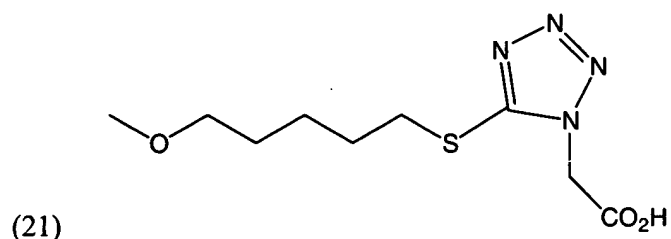
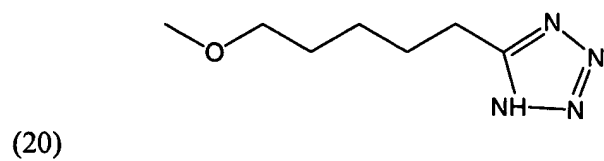
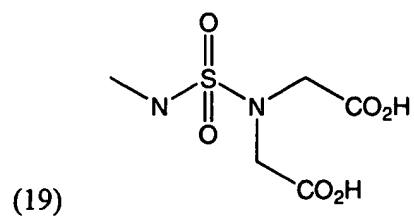
TABLE 3

R^{29}

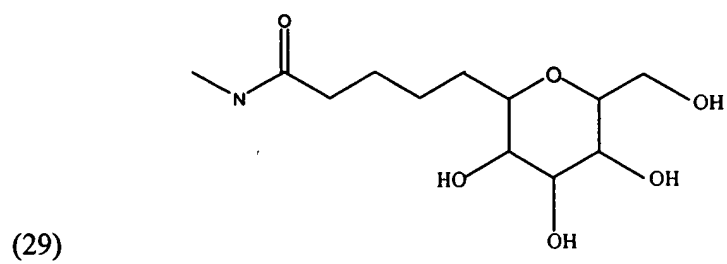
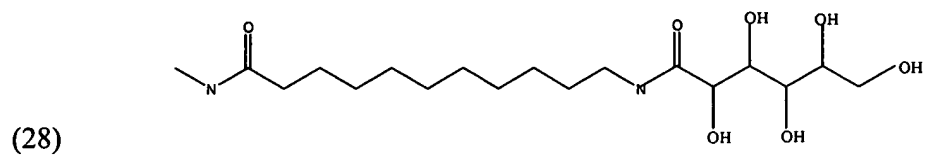
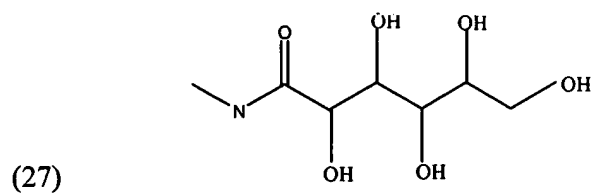
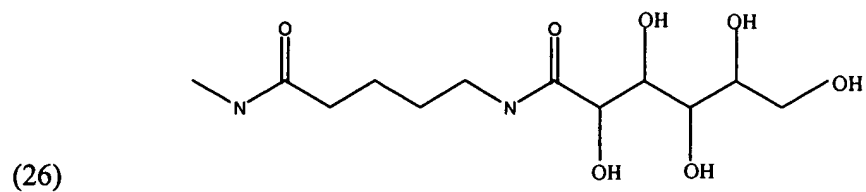
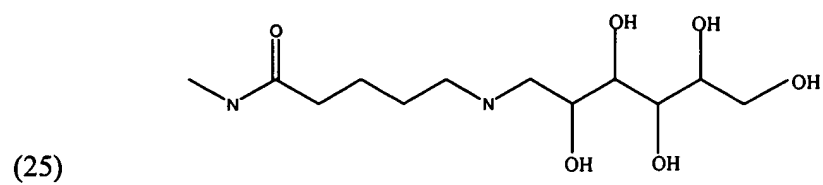


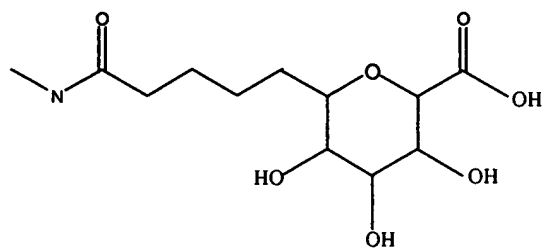
- (4)
- (5)
- (6)
- (7)
- (8)
- (9)
- (10)
- (11)
- (12)



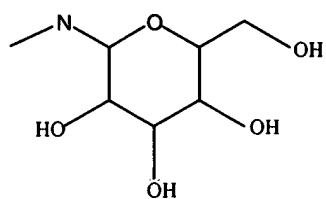


M = Co^{II, III}, Mn^{II, III}, Fe^{II, III}, Ni^{II, III},
Cr^{III}, Cu^{II}, Zn^{II}, Cd^{II}, Ga^{III}, In^{III}, V^{IV},
Ru^{II}, Pr^{IV}, Rh^{III} or Ir^{III}

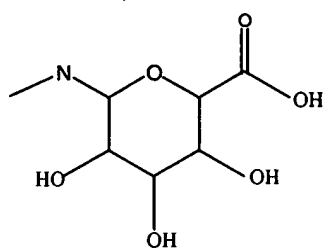


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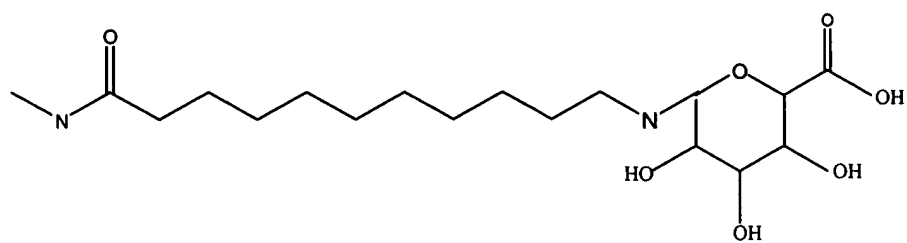
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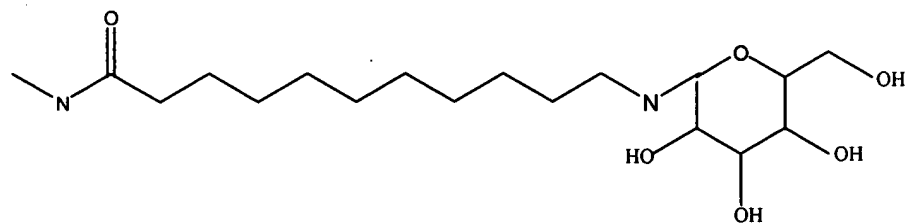
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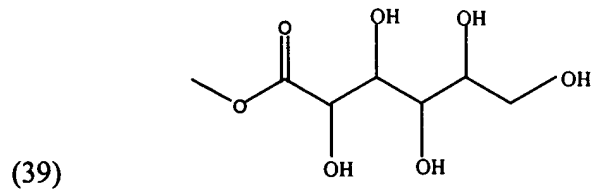
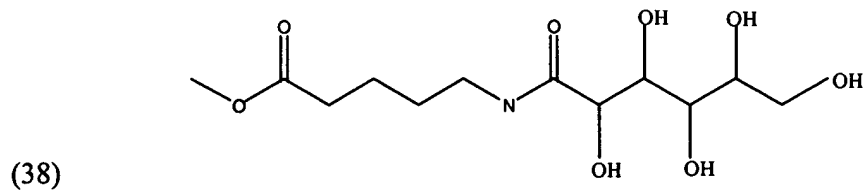
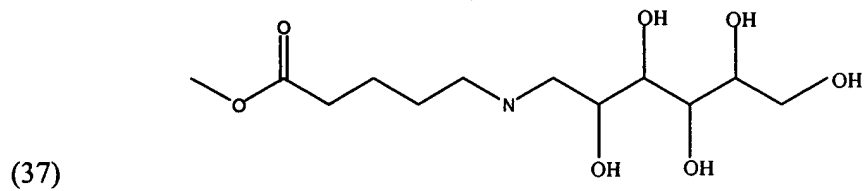
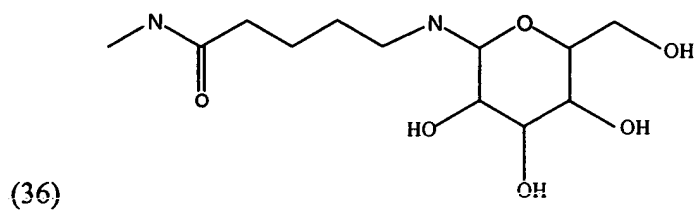
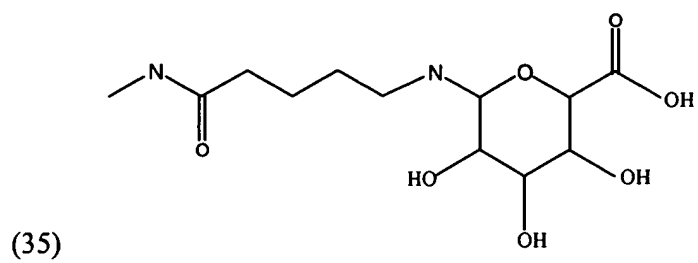
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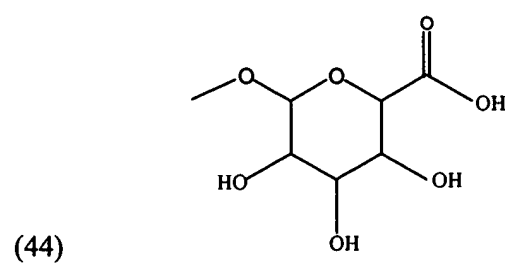
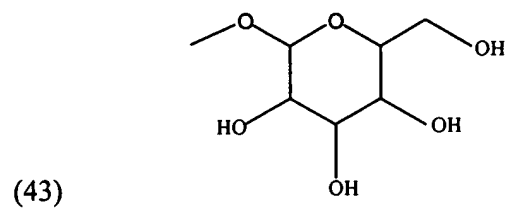
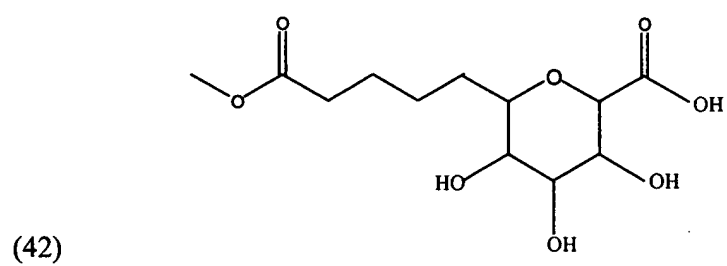
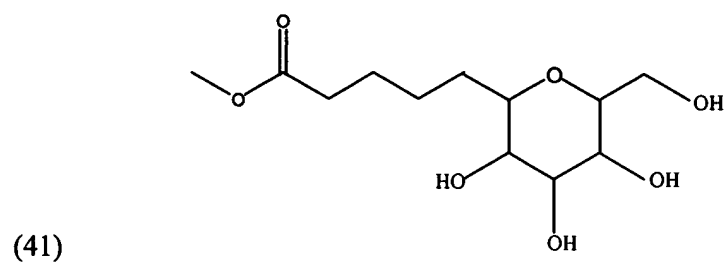
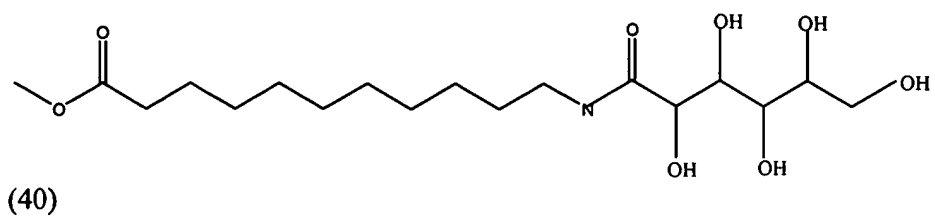


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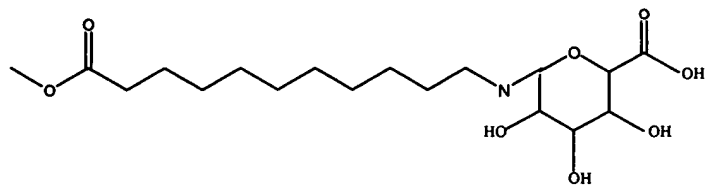


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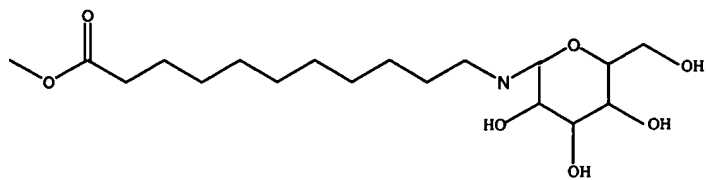




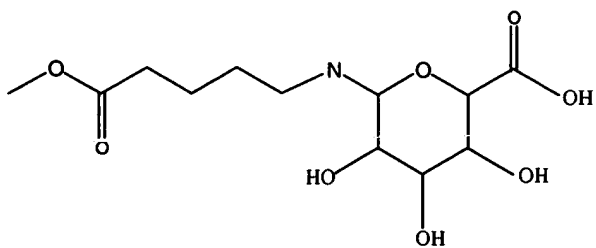
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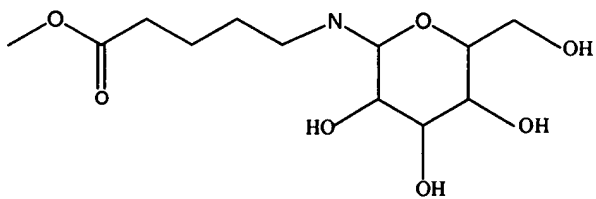
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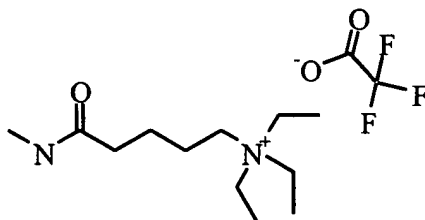
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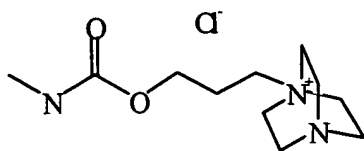
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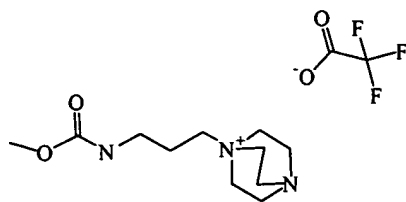
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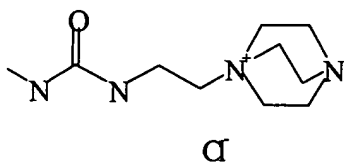
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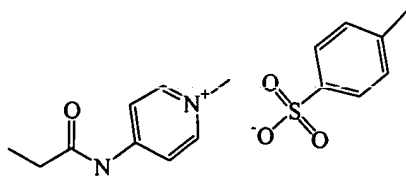
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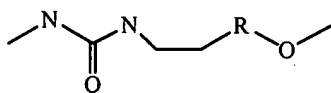
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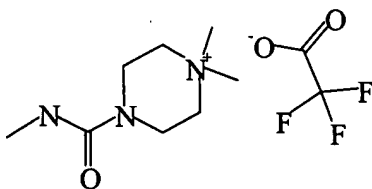
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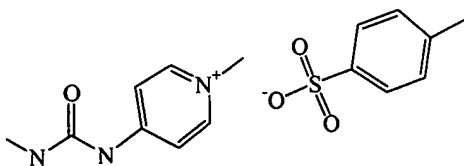
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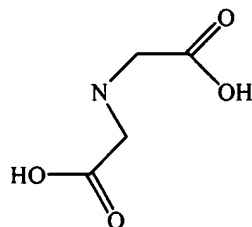
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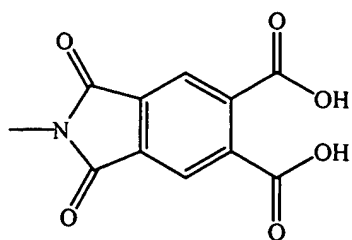


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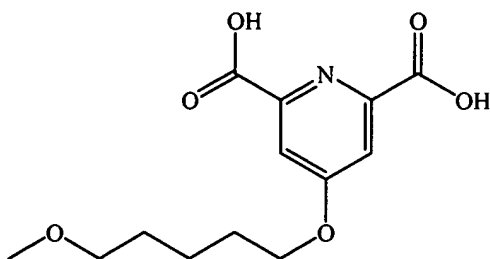


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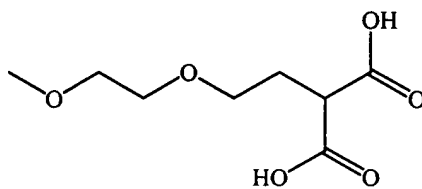




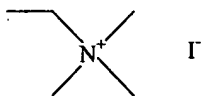
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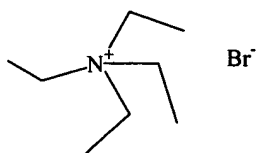
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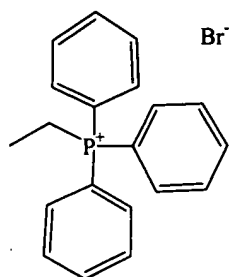
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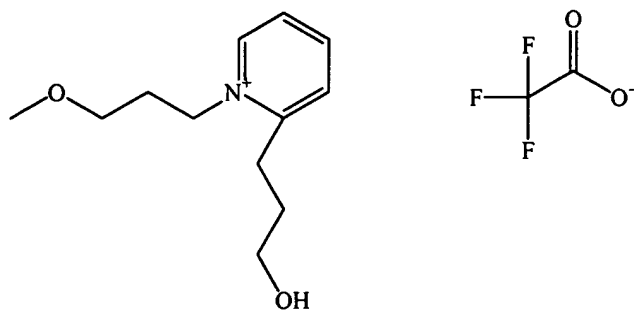
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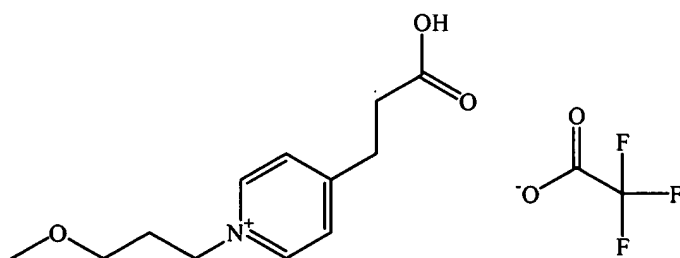
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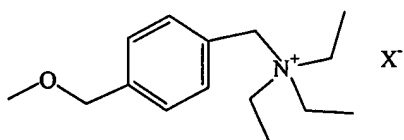
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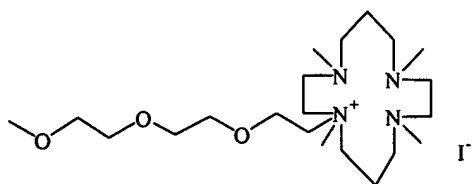
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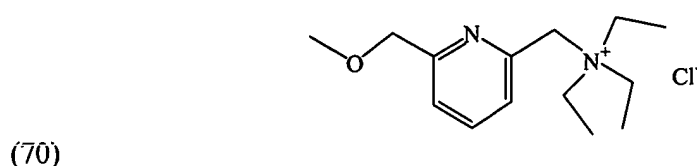
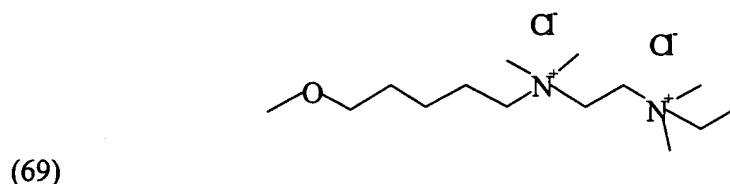
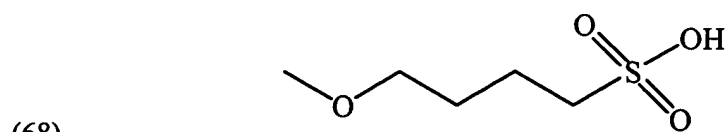
(65)



(66)



(67)



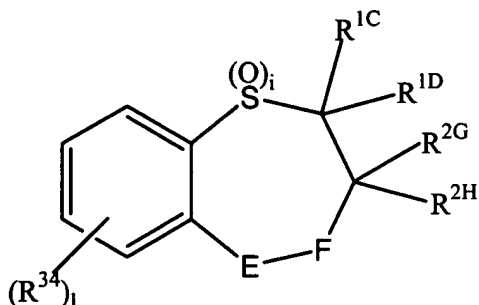
[314] Optionally, R^{29} may be selected from the following: (1) – (24), (25) – (48) or (49) – (70) from Table 3. Further, R^{29} may be acidic or contain a quaternary ammonium nitrogen. Even further, R^{29} may be selected from the following: (1) – (5), (6) – (10), (11) – (15), (16) – (20), (21) – (25), (26) – (30), (31) – (35), (36) – (40), (41) – (45), (46) – (50), (51) – (55), (56) – (60), (61) – (65), (66) – (70), or combinations thereof.

[315] In another embodiment of the compounds of Formula V, R^{25} and R^{26} are independently selected from hydrogen and methoxy.

[316] In another embodiment of the compounds of Formula V, one of R^{2E} and R^{2F} is ethyl and the other of R^{2E} and R^{2F} is n-butyl; and R^{25} and R^{26} are hydrogen.

[317] In another embodiment of the compounds of Formula V, one of R^{2E} and R^{2F} is ethyl and the other of R^{2E} and R^{2F} is n-butyl; and R^{25} and R^{26} are methoxy.

[318] Within the compounds of Formula I is another class of compounds of particular interest corresponding to Formula VII:



VII

[319] wherein:

[320] i is 0, 1 or 2; and

[321] l is 0, 1, 2, 3 or 4; and

[322] R^{1C} and R^{1D} are independently selected from hydrogen and alkyl; and

[323] R^{2G} and R^{2H} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; or

[324] R^{2G} and R^{2H} together with the carbon atom to which they are attached form a C_{3-10} cycloalkyl group; and

[325] one of E and F is NR^{30} and the other of E and F is CHR^{31} ;

[326] wherein R^{30} and R^{31} are independently selected from the group consisting of hydrogen; oxo; alkyl; cycloalkyl; aryl; heterocyclyl; acyl, thioacyl, -OR⁹, and R^{32} ;

[327] wherein the R^{30} and R^{31} alkyl; cycloalkyl; aryl; heterocyclyl radicals are independently substituted with one or more radicals independently selected from the group consisting of halogen; -CN; -NO₂; oxo; alkyl; polyalkyl; haloalkyl; hydroxyalkyl; cycloalkyl; alkenyl; alkynyl; aryl;

heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclalkyl; polyether; $-\text{OR}^{13}$; $-\text{NR}^{13}\text{R}^{14}$; $-\text{SR}^{13}$; $-\text{S}(\text{O})\text{R}^{13}$; $-\text{SO}_2\text{R}^{13}$; $-\text{SO}_3\text{R}^{13}$; $-\text{NR}^{13}\text{OR}^{14}$; $-\text{NR}^{13}\text{NR}^{14}\text{R}^{15}$; $-\text{CO}_2\text{R}^{13}$; $-\text{OM}$; $-\text{SO}_2\text{OM}$; $-\text{SO}_2\text{NR}^{13}\text{R}^{14}$; $-\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$; $-\text{C}(\text{O})\text{OM}$; $-\text{COR}^{13}$; $-\text{NR}^{13}\text{C}(\text{O})\text{R}^{14}$; $-\text{NR}^{13}\text{C}(\text{O})\text{NR}^{14}\text{R}^{15}$; $-\text{NR}^{13}\text{CO}_2\text{R}^{14}$; $-\text{OC}(\text{O})\text{R}^{13}$; $-\text{OC}(\text{O})\text{NR}^{13}\text{R}^{14}$; $-\text{NR}^{13}\text{SOR}^{14}$; $-\text{NR}^{13}\text{SO}_2\text{R}^{14}$; $-\text{NR}^{13}\text{SONR}^{14}\text{R}^{15}$; $-\text{NR}^{13}\text{SO}_2\text{NR}^{14}\text{R}^{15}$; $-\text{PR}^{13}\text{R}^{14}$; $-\text{P}(\text{O})\text{R}^{13}\text{R}^{14}$; $-\text{P}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$; $-\text{P}(\text{OR}^{13})\text{OR}^{14}$; $-\text{S}^+\text{R}^{13}\text{R}^{14}\text{A}^-$; and $-\text{N}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$; and wherein the R^{30} and R^{31} alkyl; cycloalkyl; aryl; heterocyclyl radicals are independently substituted with one or more radicals independently selected from the group consisting of halogen; $-\text{CN}$; $-\text{NO}_2$; oxo; alkyl; polyalkyl; haloalkyl; hydroxyalkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclalkyl; polyether; $-\text{OR}^{13}$; $-\text{NR}^{13}\text{R}^{14}$; $-\text{SR}^{13}$; $-\text{S}(\text{O})\text{R}^{13}$; $-\text{SO}_2\text{R}^{13}$; $-\text{SO}_3\text{R}^{13}$; $-\text{NR}^{13}\text{OR}^{14}$; $-\text{NR}^{13}\text{NR}^{14}\text{R}^{15}$; $-\text{CO}_2\text{R}^{13}$; $-\text{OM}$; $-\text{SO}_2\text{OM}$; $-\text{SO}_2\text{NR}^{13}\text{R}^{14}$; $-\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$; $-\text{C}(\text{O})\text{OM}$; $-\text{COR}^{13}$; $-\text{NR}^{13}\text{C}(\text{O})\text{R}^{14}$; $-\text{NR}^{13}\text{C}(\text{O})\text{NR}^{14}\text{R}^{15}$; $-\text{NR}^{13}\text{CO}_2\text{R}^{14}$; $-\text{OC}(\text{O})\text{R}^{13}$; $-\text{OC}(\text{O})\text{NR}^{13}\text{R}^{14}$; $-\text{NR}^{13}\text{SOR}^{14}$; $-\text{NR}^{13}\text{SO}_2\text{R}^{14}$; $-\text{NR}^{13}\text{SONR}^{14}\text{R}^{15}$; $-\text{NR}^{13}\text{SO}_2\text{NR}^{14}\text{R}^{15}$; $-\text{PR}^{13}\text{R}^{14}$; $-\text{P}(\text{O})\text{R}^{13}\text{R}^{14}$; $-\text{P}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$; $-\text{P}(\text{OR}^{13})\text{OR}^{14}$; $-\text{S}^+\text{R}^{13}\text{R}^{14}\text{A}^-$; and $-\text{N}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$; and

[328] wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclalkyl, and polyether substituents of the R^{30} and R^{31} radicals optionally may be further substituted with one or more radicals selected from the group consisting of $-\text{CN}$; halogen; hydroxy; oxo; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclalkyl; quaternary heterocyclyl; $-\text{OR}^7$; $-\text{NR}^7\text{R}^8$; $-\text{SR}^7$; $-\text{S}(\text{O})\text{R}^7$; $-\text{SO}_2\text{R}^7$; $-\text{SO}_3\text{R}^7$; $-\text{CO}_2\text{R}^7$; $-\text{CONR}^7\text{R}^8$; $-\text{N}^+\text{R}^7\text{R}^8\text{R}^9\text{A}^-$; $-\text{P}(\text{O})\text{R}^7\text{R}^8$; $-\text{PR}^7\text{R}^8$; $-\text{P}^+\text{R}^7\text{R}^8\text{R}^9\text{A}^-$; and $-\text{P}(\text{O})(\text{OR}^7)\text{OR}^8$; and

- [329] wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether substituents of the R^{30} and R^{31} radicals optionally may have one or more carbons replaced by -O-; -NR⁷-; -N⁺R⁷R⁸A⁻; -S-; -SO-; -SO₂-; -S⁺R⁷A⁻; -PR⁷-; -P(O)R⁷-; -P⁺R⁷R⁸A⁻; or phenylene; and
- [330] wherein R⁷ and R⁸ are independently selected from the group consisting of hydrogen; and alkyl; and
- [331] wherein R⁹, R¹⁰, and R^w are independently selected from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; alkylammoniumalkyl; arylalkyl; heterocyclylalkyl; carboxyalkyl; alkoxyalkyl; carboalkoxyalkyl; carboxyaryl; carboxyheterocyclyl; amino; alkylamino; carboxyalkylamino; alkoxyalkylamino; and acyl; and
- [332] wherein R¹¹ and R¹² are independently selected from the group consisting of hydrogen; -CN; halogen; oxo; alkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; carboxyalkyl; alkoxyalkyl; carboalkoxyalkyl; cycloalkyl; cycloalkenyl; haloalkyl; hydroxyalkyl; cyanoalkyl; -OR⁹; -NR⁹R¹⁰; -SR⁹; -S(O)R⁹; -SO₂R⁹; -SO₃R⁹; -CO₂R⁹; and -CONR⁹R¹⁰; or
- [333] R¹¹ and R¹² together with the carbon atom to which they are attached form a cyclic ring; and
- [334] wherein R¹³, R¹⁴, and R¹⁵ are independently selected from the group consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminoalkyl;

aminocarbonylalkyl; alkylaminocarbonylalkyl;
carboxyalkylaminocarbonylalkyl; and polyether; or

[335] wherein R^{13} and R^{14} together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocyclyl that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy, and quaternary salts; or

[336] wherein R^{14} and R^{15} together with the nitrogen atom to which they are attached form a cyclic ring; and

[337] wherein the R^{13} , R^{14} , and R^{15} alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may be substituted with one or more radicals selected from the group consisting of halogen; -CN; sulfo; oxo; alkyl; haloalkyl; hydroxyalkyl; sulfoalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; quaternary heterocyclylalkyl; carboxy; carboxyalkyl; guanidiny; -OR¹⁶; -NR⁹R¹⁰; -N⁺R⁹R¹⁰R^wA⁻; -SR¹⁶; -S(O)R⁹; -SO₂R⁹; -SO₃R¹⁶; -CO₂R¹⁶; -CONR⁹R¹⁰; -SO₂NR⁹R¹⁰; -PO(OR¹⁶)OR¹⁷; -P⁹R¹⁰; -P⁺R⁹R¹⁰R¹¹A⁻; -S⁺R⁹R¹⁰A⁻; and carbohydrate residue; and

[338] wherein the R^{13} , R^{14} , and R^{15} alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may have one or more carbons replaced by -O-; -NR⁹-; -N⁺R⁹R¹⁰A⁻; -S-; -

SO⁻; -SO₂⁻; -S⁺R⁹A⁻; -PR⁹⁻; -P⁺R⁹R¹⁰A⁻; -P(O)R⁹⁻; phenylene; carbohydrate residue; amino acid residue; peptide residue; or polypeptide residue; and

[339] wherein R¹⁶ and R¹⁷ are independently selected from the group consisting of R⁹ and M; and

[340] wherein A is a pharmaceutically acceptable cation and M is a pharmaceutically acceptable cation; and

[341] R³² is selected from the group consisting of cycloalkyl, aryl and heterocyclyl, wherein said cycloalkyl, aryl and heterocyclyl are substituted with -N(H)-X-R³³ or -O-X-R³³ and wherein:

[342] X is selected from the group consisting of:

[343] -(C=O)_s-alkyl-;

[344] -(C=O)_s-alkyl-NH-;

[345] -(C=O)_s-alkyl-O-;

[346] -(C=O)_s-alkyl-(C=O)_t; and

[347] a covalent bond;

[348] R³³ is selected from selected from the group consisting of monosaccharides, disaccharides, and polysaccharides, wherein said monosaccharides, disaccharides, and polysaccharides may be protected with one or more sugar protecting groups;

[349] s and t are independently 0 or 1; and

[350] one or more R³⁴ radicals are independently selected from the group consisting of R³², hydrogen; halogen; -CN; -NO₂; alkyl; cycloalkyl; polyalkyl; haloalkyl; hydroxyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; acyloxy;

0991223 072501

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-OR¹³; -NR¹³R¹⁴; -SR¹³; -S(O)R¹³; -S(O)2R¹³; -SO3R¹³; -S⁺R¹³R¹⁴
A⁻; -NR¹³OR¹⁴; -NR¹³NR¹⁴R¹⁵; -CO2R¹³; -OM; -SO2OM; -SO2NR¹³
R¹⁴; -NR¹⁴C(O)R¹³; -C(O)NR¹³R¹⁴; -C(O)OM; -COR¹³; -OR¹⁸; -
S(O)_nNR¹³R¹⁴; -NR¹³R¹⁸; -NR¹⁸OR¹⁴; -N⁺R¹³R¹⁴R¹⁵A⁻; -PR¹³R¹⁴;
-P(O)R¹³R¹⁴; -P⁺R¹³R¹⁴R¹⁵A⁻; amino acid residue; peptide
residue; polypeptide residue; and carbohydrate residue;

[351] wherein the R³⁴ alkyl; cycloalkyl; polyalkyl; haloalkyl; hydroxyalkyl;
alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclalkyl;
polyether; acyloxy radicals optionally may be further substituted with one
or more radicals selected from the group consisting of halogen; -CN; oxo;
-OR¹⁶; -NR⁹R¹⁰; -N⁺R⁹R¹⁰R^wA⁻; -SR¹⁶; -S(O)R⁹; -SO2R⁹; -SO3R¹⁶
; -CO2R¹⁶; -CONR⁹R¹⁰; -SO2NR⁹R¹⁰; -PO(OR¹⁶)OR¹⁷; -P⁹R¹⁰; -P⁺R⁹
R¹¹R¹²A⁻; -S⁺R⁹R¹⁰A⁻; and carbohydrate residue; and

[352] wherein the R³⁴ quaternary heterocyclyl radical optionally may be
substituted with one or more radicals selected from the group consisting
of halogen; -CN; -NO2; oxo; alkyl; cycloalkyl; polyalkyl; haloalkyl;
hydroxyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl;
heterocyclalkyl; polyether; -OR¹³; -NR¹³R¹⁴; -SR¹³; -S(O)R¹³; -SO2
R¹³; -SO3R¹³; -NR¹³OR¹⁴; -NR¹³NR¹⁴R¹⁵; -CO2R¹³; OM; -SO2
OM; -SO2NR¹³R¹⁴; -C(O)NR¹³R¹⁴; -C(O)OM; -COR¹³; -P(O)R¹³R¹⁴;
-P¹³R¹⁴; -P⁺R¹³R¹⁴R¹⁵A⁻; -P(OR¹³)OR¹⁴; -S⁺R¹³R¹⁴A⁻; -N⁺R¹³
R¹⁴R¹⁵A⁻; and carbohydrate residue; and

[353] wherein the R³⁴ radicals comprising carbon optionally may have one or
more carbons replaced by -O-; -NR¹³-; -N⁺R¹³R¹⁴A⁻; -S-; -SO-; -SO2-;
-S⁺R¹³A⁻; -PR¹³-; -P(O)R¹³-; -PR¹³R¹⁴; -P⁺R¹³R¹⁴A⁻; phenylene;
amino acid residue; peptide residue; polypeptide residue; carbohydrate

residue; polyether; or polyalkyl; wherein said phenylene; amino acid residue; peptide residue; polypeptide residue; carbohydrate residue; and polyalkyl optionally may have one or more carbons replaced by -O-; -NR⁹-; -N⁺R⁹R¹⁰A⁻-; -S-; -SO-; -SO₂-; -S⁺R⁹A⁻-; -PR⁹-; -P⁺R⁹R¹⁰A⁻-; or -P(O)R⁹-; and

[354] wherein R¹⁸ is selected from the group consisting of alkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclalkyl; acyl; alkoxycarbonyl; arylalkoxycarbonyl; and heterocyclalkoxycarbonyl; and

[355] wherein the R¹⁸ alkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclalkyl; acyl; alkoxycarbonyl; arylalkoxycarbonyl; and heterocyclalkoxycarbonyl radicals optionally may be substituted with one or more radicals selected from the group consisting of halogen; -CN; NO₂; oxo; -OR⁹; -NR⁹R¹⁰; -N⁺R⁹R¹¹R¹²A⁻; -SR⁹; -S(O)R⁹; -SO₂R⁹; -SO₃R⁹; -CO₂R⁹; -CONR⁹R¹⁰; -SO₂OM; -SO₂NR⁹R¹⁰; -PR⁹R¹⁰; -P(OR¹³)OR¹⁴; -PO(OR¹⁶)OR¹⁷; and -C(O)OM; or

[356] a pharmaceutically acceptable salt, solvate, or prodrug thereof;

[357] provided that at least one of R³⁰, R³¹ and R³⁴ is R³².

[358] Preferably, R³² is phenyl substituted with -N(H)-X-R³³ or -O-X-R³³ wherein:

[359] X is selected from the group consisting of:

[360] -(C=O)_s-alkyl-;

[361] -(C=O)_s-alkyl-NH-;

[362] -(C=O)_s-alkyl-O-;

- [363] $-(C=O)_s\text{-alkyl-(C=O)}_t$; and
- [364] a covalent bond;
- [365] R^{33} is selected from selected from the group consisting of monosaccharides, disaccharides, and polysaccharides; and
- [366] s and t are independently 0 or 1.
- [367] In one embodiment, R^{32} is phenyl substituted at the para-position with -N(H)-X- R^{33} or -O-X- R^{33} wherein:
- [368] X is selected from the group consisting of:
 - [369] $-(C=O)_s\text{-alkyl-}$;
 - [370] $-(C=O)_s\text{-alkyl-NH-}$;
 - [371] $-(C=O)_s\text{-alkyl-O-}$;
 - [372] $-(C=O)_s\text{-alkyl-(C=O)}_t$; and
 - [373] a covalent bond; and
- [374] R^{33} is selected from selected from the group consisting of monosaccharides, disaccharides, and polysaccharides; and
- [375] s and t are independently 0 or 1.
- [376] In another embodiment, R^{32} is phenyl substituted at the meta-position with -N(H)-X- R^{33} or -O-X- R^{33} wherein:
- [377] X is selected from the group consisting of:
 - [378] $-(C=O)_s\text{-alkyl-}$;
 - [379] $-(C=O)_s\text{-alkyl-NH-}$;
 - [380] $-(C=O)_s\text{-alkyl-O-}$;

[381] $-(C=O)_s\text{-alkyl-(C=O)}_t$; and

[382] a covalent bond; and

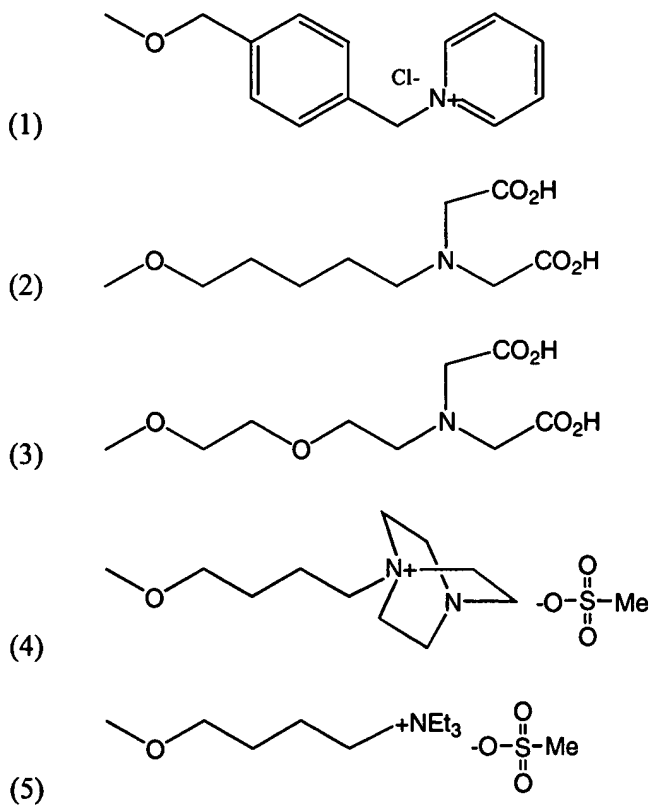
[383] R^{33} is selected from the group consisting of monosaccharides, disaccharides, and polysaccharides; and

[384] s and t are independently 0 or 1;

[385] In another embodiment, R^{32} is phenyl substituted with a radical selected from the group consisting of:

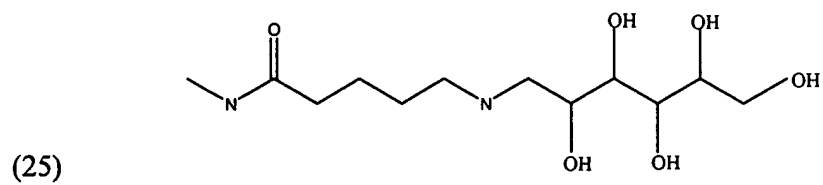
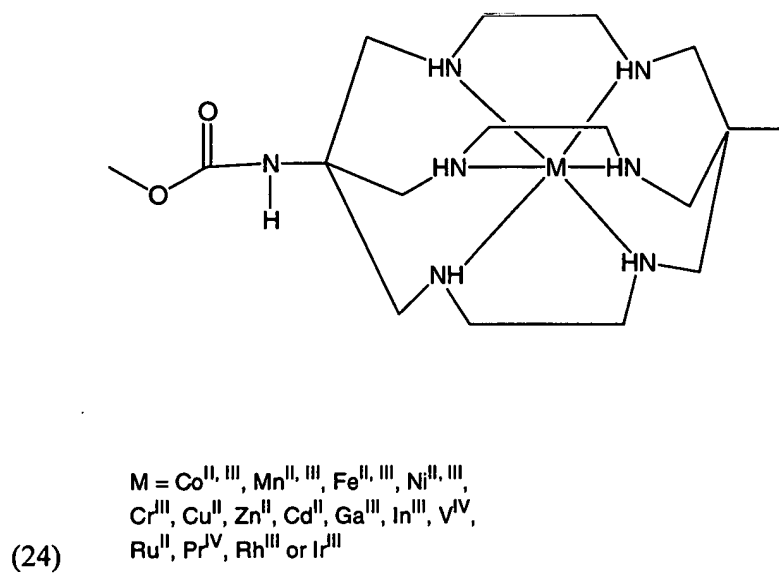
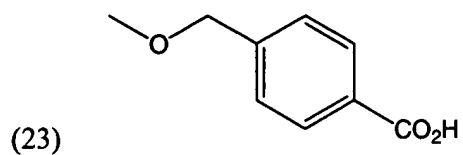
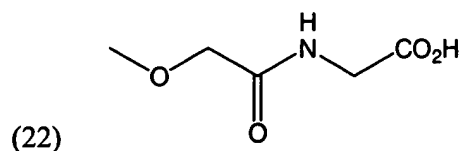
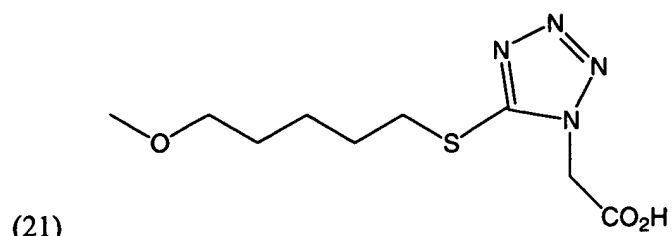
TABLE 4

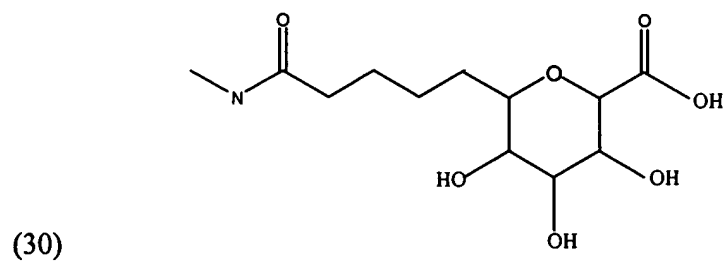
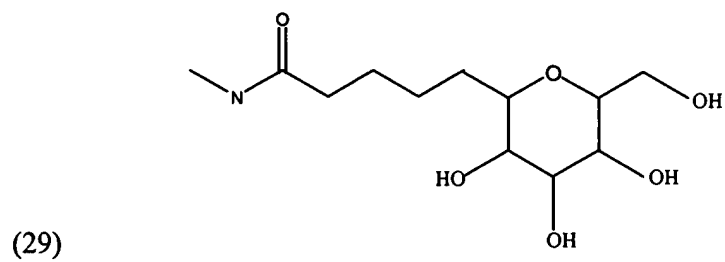
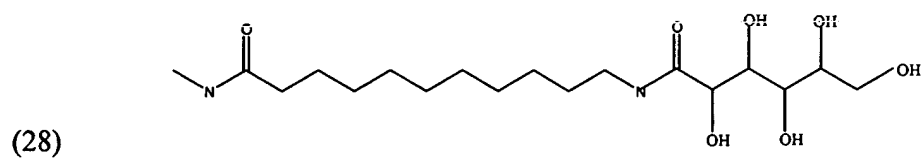
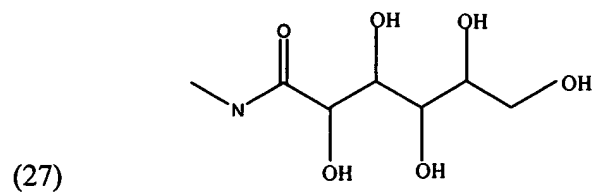
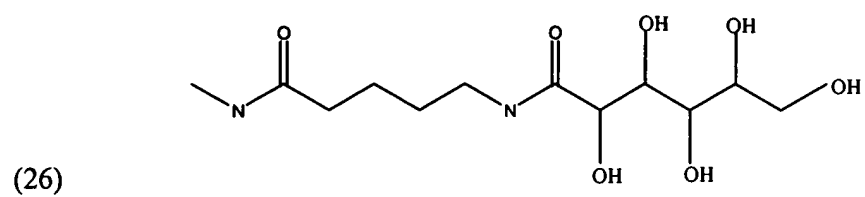
R^{32}

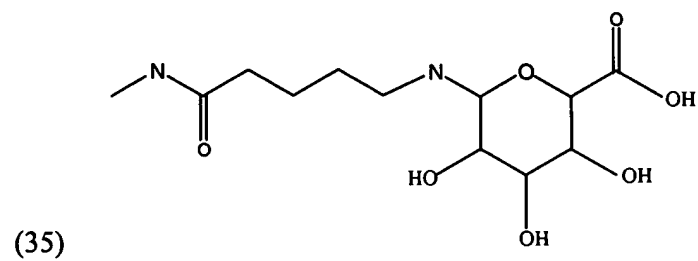
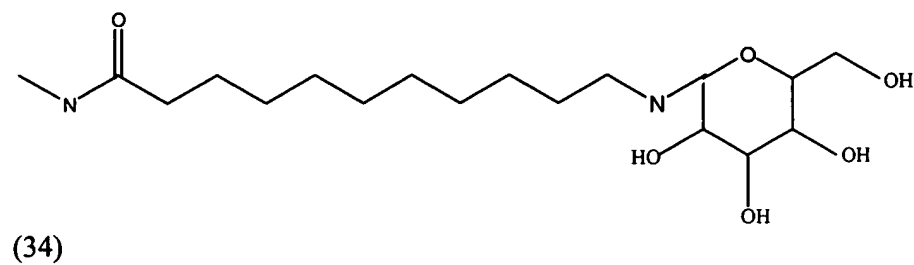
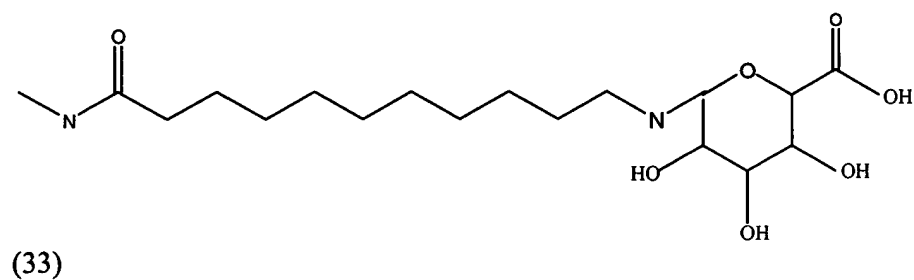
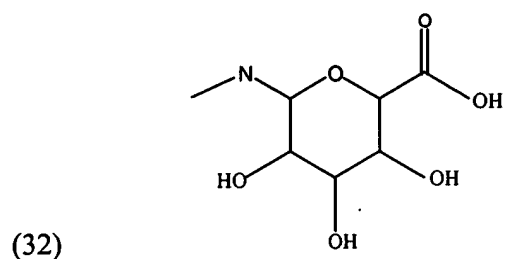
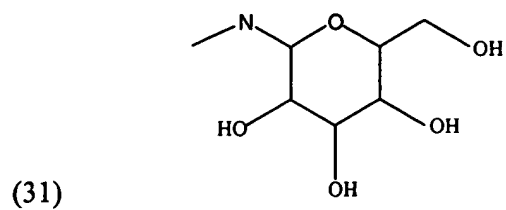


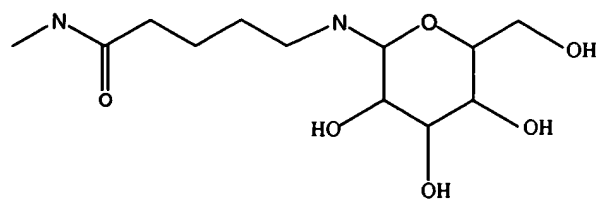
- (6)
- (7)
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- (9)
- (10)
- (11)
- (12)
- (13)
- (14)



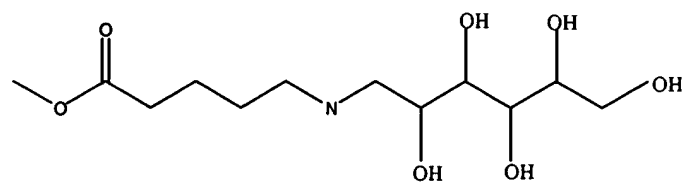




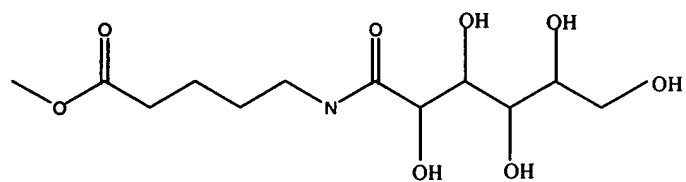




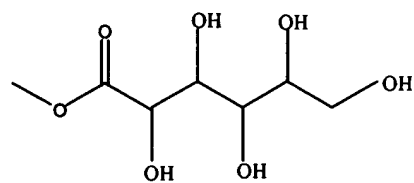
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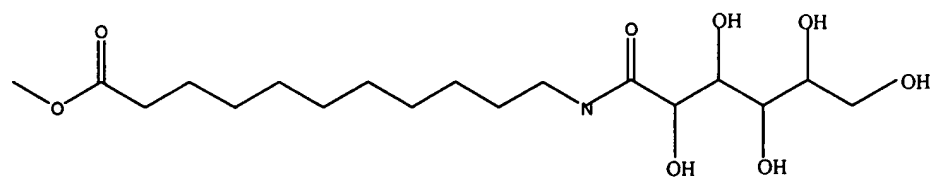
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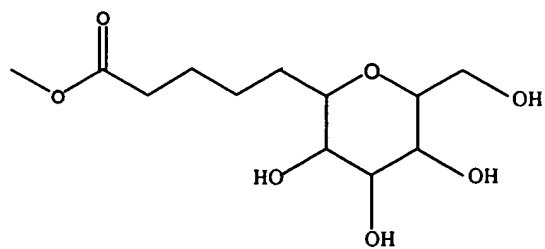
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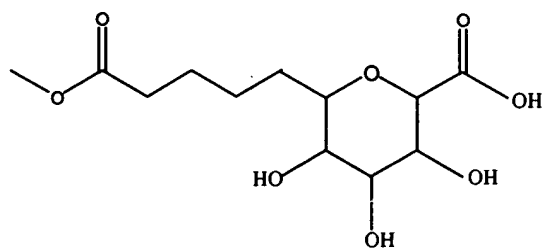
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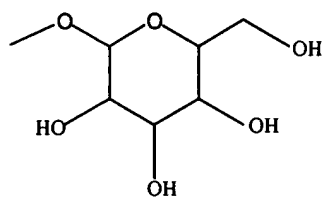
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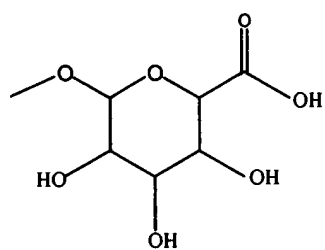
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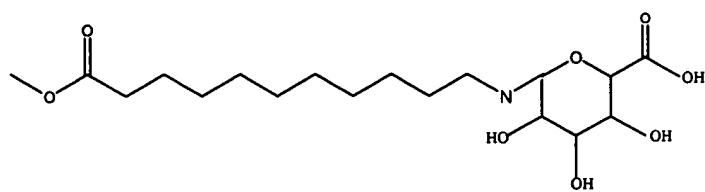
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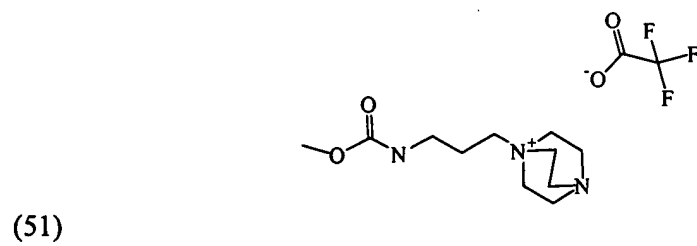
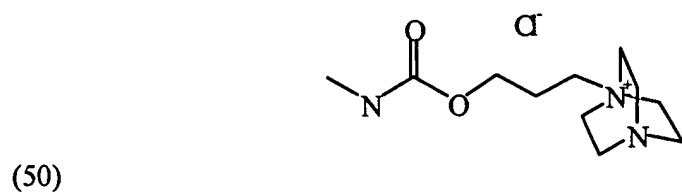
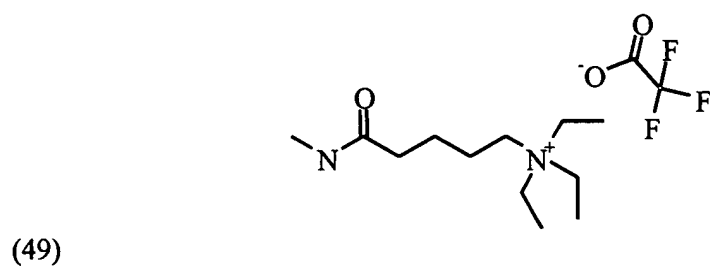
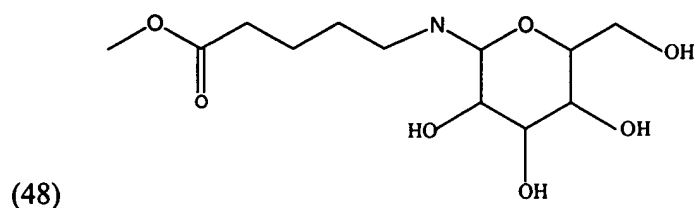
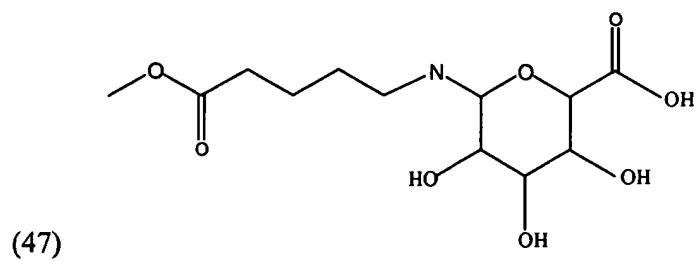
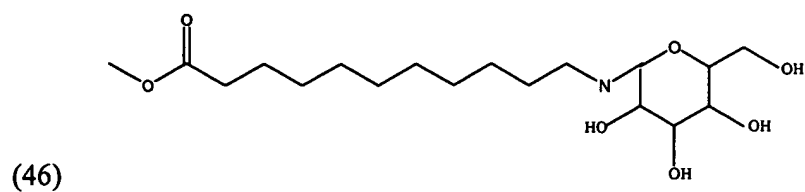
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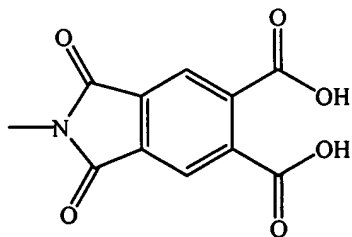
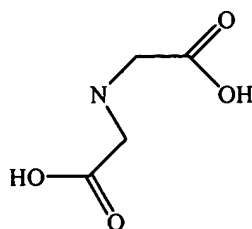
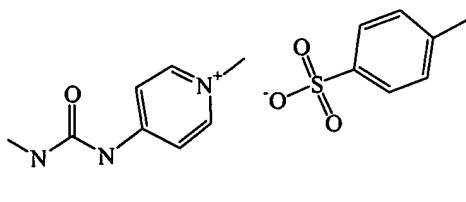
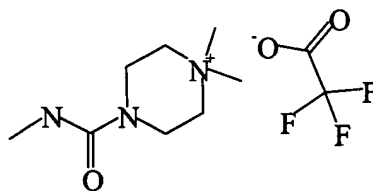
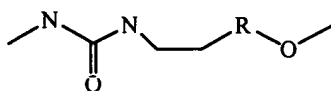
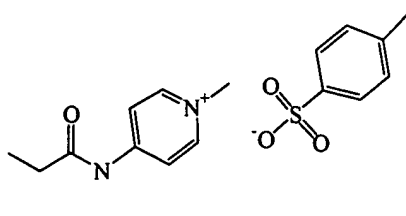
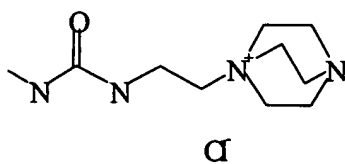


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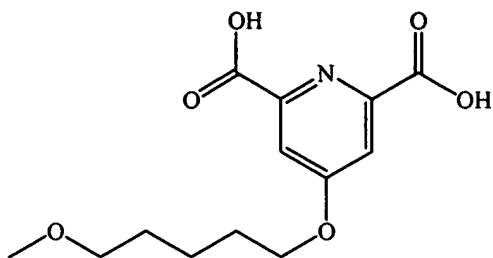


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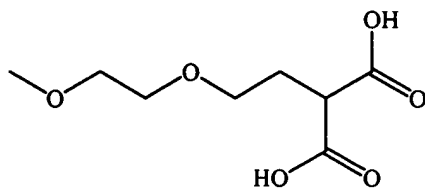




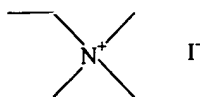
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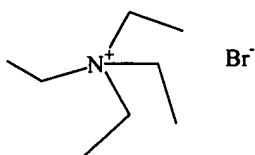
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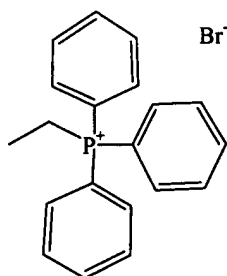
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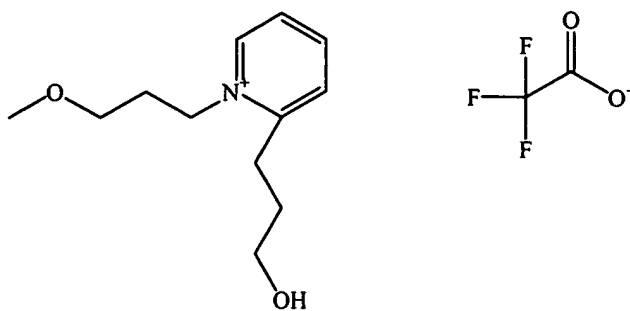


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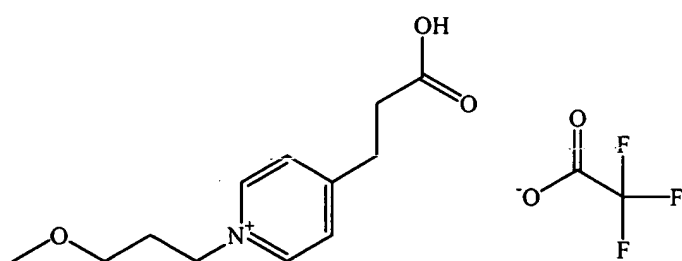


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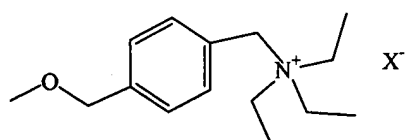




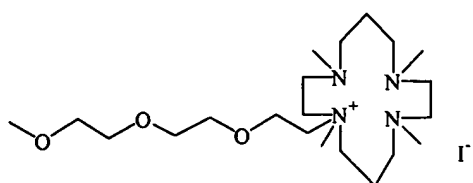
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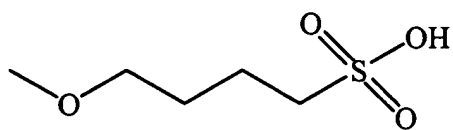
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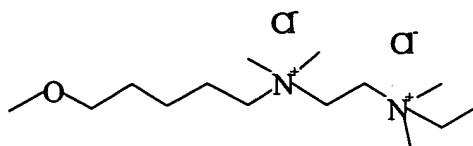
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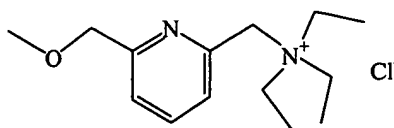
(67)



(68)



(69)



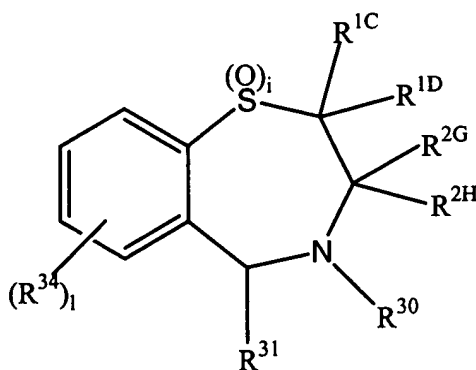
(70)

[386] Optionally, R^{32} may be selected from the following: (1) – (24), (25) – (48) or (49) – (70) from Table 4. Further, R^{32} may be acidic or contain a quaternary ammonium nitrogen. Even further, R^{32} may be selected from the following: (1) – (5), (6) – (10), (11) – (15), (16) – (20), (21) – (25), (26) – (30), (31) – (35), (36) – (40), (41) – (45), (46) – (50), (51) – (55), (56) – (60), (61) – (65), (66) – (70), or combinations thereof.

[387] In another embodiment of the compounds of Formula VII, R^{30} is R^{32} ; and R^{31} is selected from the group consisting of hydrogen and alkyl.

[388] In another embodiment of the compounds of Formula VII, R^{30} is selected from the group consisting of hydrogen and alkyl; and R^{31} is R^{32} .

[389] Within the compounds of Formula VII is a class of compounds of specific interest corresponding to Formula VIIA:



VIIA

[390] wherein:

[391] i is 0, 1 or 2; and

[392] l is 0, 1, 2, 3 or 4; and

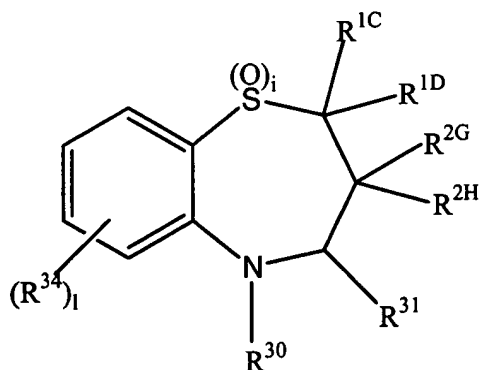
[393] R^{1C} and R^{1D} are independently selected from hydrogen and alkyl; and

[394] R^{2G} and R^{2H} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; or

[395] R^{2G} and R^{2H} together with the carbon atom to which they are attached form a C_{3-7} cycloalkyl group; and

[396] i , l , R^{30} , R^{31} and R^{34} are as previously defined above for compounds of Formula VII.

[397] Within the compounds of Formula VII is a class of compounds of specific interest corresponding to Formula VIIB:



[398] wherein:

[399] i is 0, 1 or 2; and

[400] l is 0, 1, 2, 3 or 4; and

[401] R^{1C} and R^{1D} are independently selected from hydrogen and alkyl; and

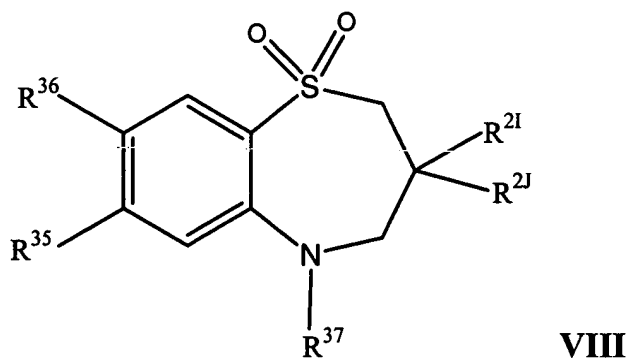
[402] R^{2G} and R^{2H} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; or

[403] R^{2G} and R^{2H} together with the carbon atom to which they are attached form a C_{3-7} cycloalkyl group; and

[404] i, l, R^{30} , R^{31} and R^{34} are as previously defined above for compounds of Formula VII.

[405]

[406] Within the compounds of Formula VII is a class of compounds of particular interest corresponding to Formula VIII:



[407] wherein:

[408] R^{2I} and R^{2J} are independently selected from C_{1-6} alkyl; and

[409] R^{35} is selected from the group consisting of halogen and R^{38} ;

[410] R^{36} is selected from the group consisting of hydroxy, alkoxy, and R^{38} ;

[411] wherein R^{38} is selected from the group consisting of cycloalkyl, aryl and heterocyclyl, wherein said cycloalkyl, aryl and heterocyclyl are substituted with $-N(H)-X-R^{39}$ or $-O-X-R^{39}$ and wherein:

[412] X is selected from the group consisting of:

[413] $-(C=O)_u$ -alkyl-;

[414] $-(C=O)_u$ -alkyl-NH-;

[415] $-(C=O)_u$ -alkyl-O-;

- [416] $-(C=O)_u\text{-alkyl-(C=O)}_v$; and
- [417] a covalent bond; and
- [418] R^{39} is selected from selected from the group consisting of monosaccharides, disaccharides, and polysaccharides, wherein said monosaccharides, disaccharides, and polysaccharides may be protected with one or more sugar protecting groups; and
- [419] u and v are independently 0 or 1; and
- [420] R^{37} is unsubstituted phenyl or R^{38} ; or
- [421] a pharmaceutically acceptable salt, solvate, or prodrug thereof;
- [422] provided that at least one of R^{35} , R^{36} and R^{37} is R^{38} .
- [423] Preferably, R^{38} is phenyl substituted with $-N(H)\text{-X-R}^{39}$ or $-O\text{-X-R}^{39}$ wherein:
- [424] X is selected from the group consisting of:
- [425] $-(C=O)_u\text{-alkyl-}$;
- [426] $-(C=O)_u\text{-alkyl-NH-}$;
- [427] $-(C=O)_u\text{-alkyl-O-}$;
- [428] $-(C=O)_u\text{-alkyl-(C=O)}_v$; and
- [429] a covalent bond; and
- [430] R^{39} is selected from selected from the group consisting of monosaccharides, disaccharides, and polysaccharides; and
- [431] u and v are independently 0 or 1.
- [432]

[433] In one embodiment, R^{38} is phenyl substituted at the para-position with - $N(H)-X-R^{39}$ or - $O-X-R^{39}$ wherein:

[434] X is selected from the group consisting of:

[435] $-(C=O)_u$ -alkyl-;

[436] $-(C=O)_u$ -alkyl-NH-;

[437] $-(C=O)_u$ -alkyl-O-;

[438] $-(C=O)_u$ -alkyl- $(C=O)_v$; and

[439] a covalent bond; and

[440] R^{39} is selected from selected from the group consisting of monosaccharides, disaccharides, and polysaccharides; and

[441] u and v are independently 0 or 1.

[442] In another embodiment, R^{38} is phenyl substituted at the meta-position with - $N(H)-X-R^{39}$ or - $O-X-R^{39}$ wherein:

[443] X is selected from the group consisting of:

[444] $-(C=O)_u$ -alkyl-;

[445] $-(C=O)_u$ -alkyl-NH-;

[446] $-(C=O)_u$ -alkyl-O-;

[447] $-(C=O)_u$ -alkyl- $(C=O)_v$; and

[448] a covalent bond; and

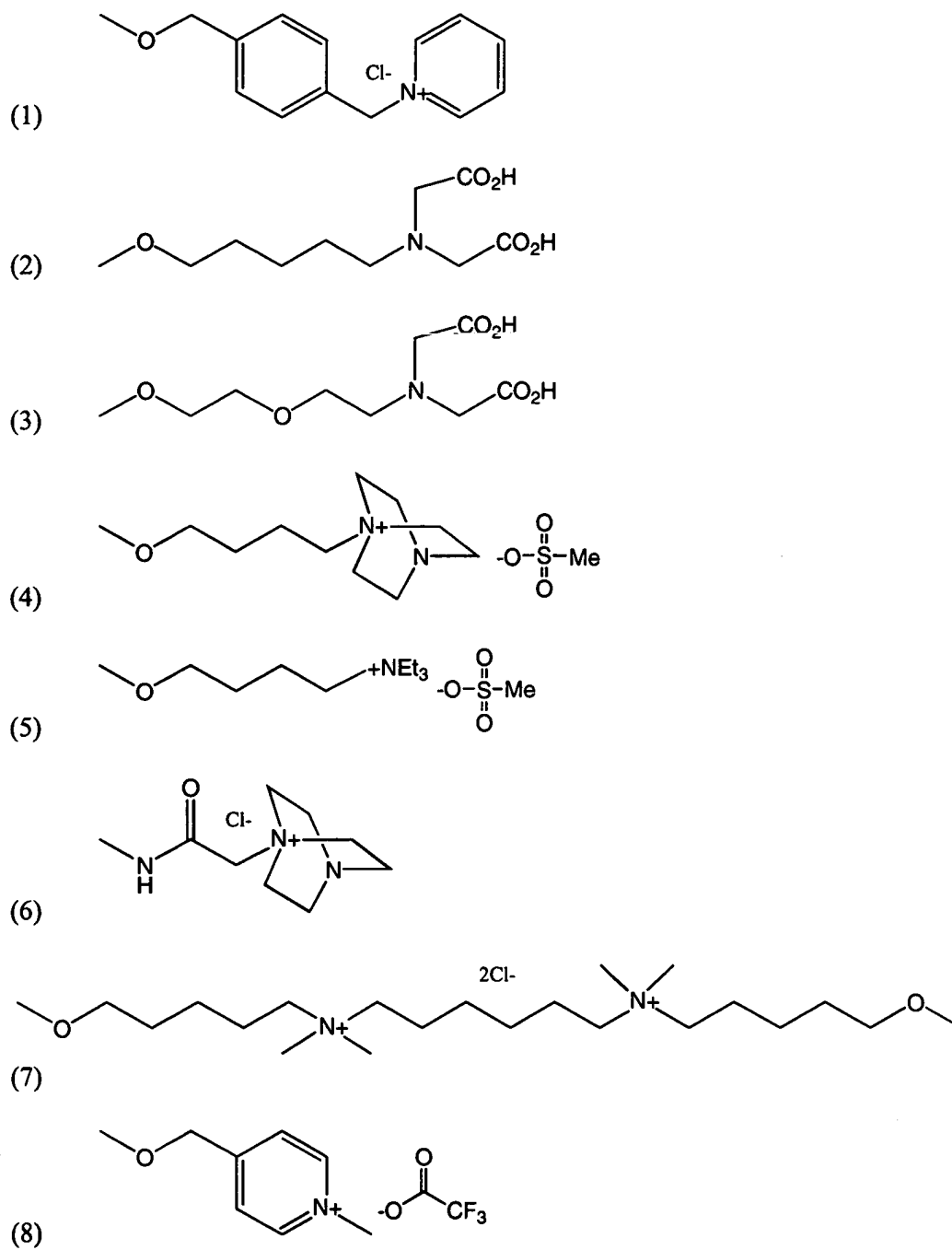
[449] R^{39} is selected from selected from the group consisting of monosaccharides, disaccharides, and polysaccharides; and

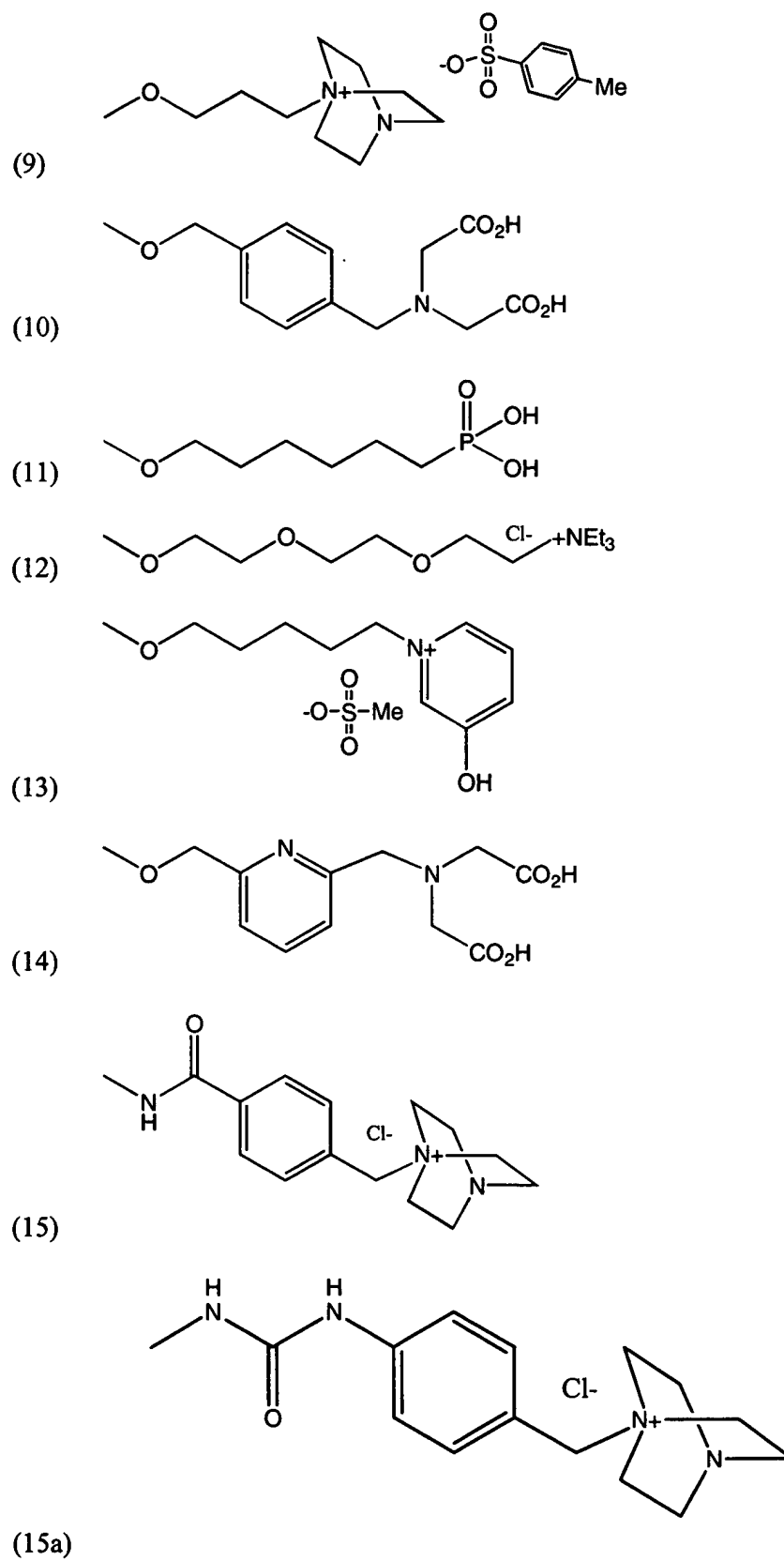
[450] u and v are independently 0 or 1.

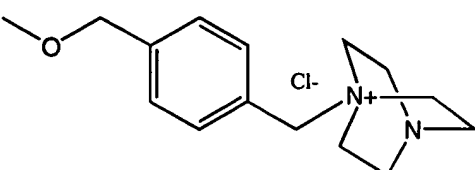
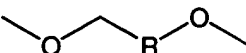
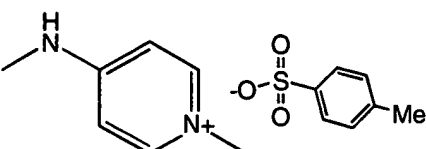
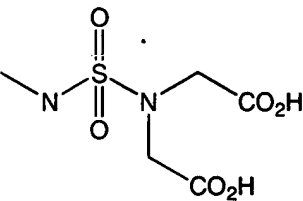
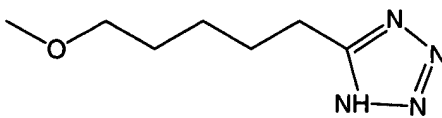
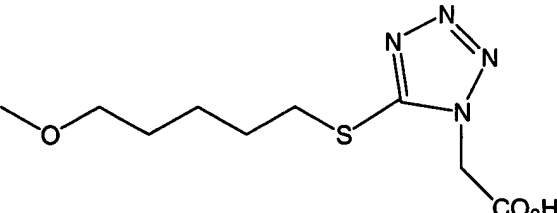
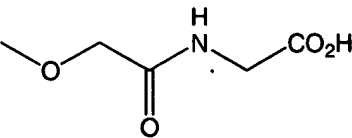
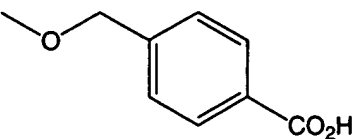
[451] In another embodiment, R^{38} is phenyl substituted with a radical selected from the group consisting of:

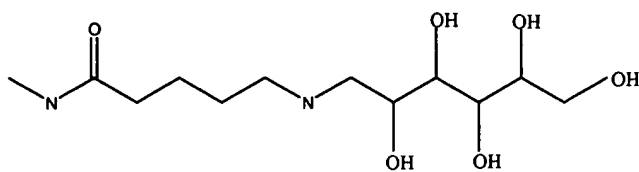
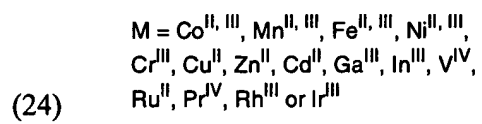
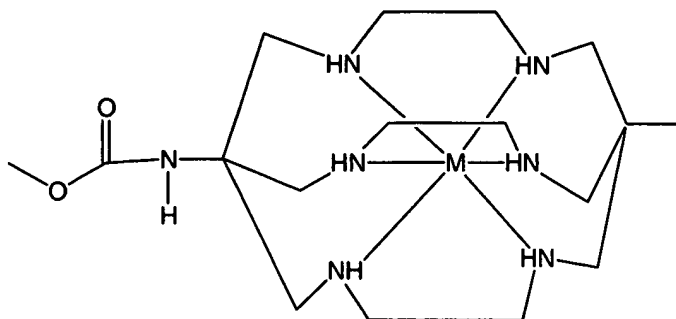
TABLE 5

R^{38}

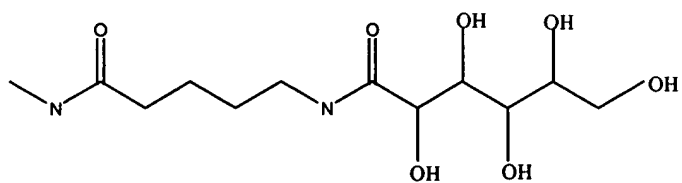




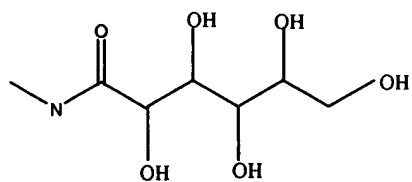
- (16) 
- (17)  R = 1000 MW PEG
- (18) 
- (19) 
- (20) 
- (21) 
- (22) 
- (23) 



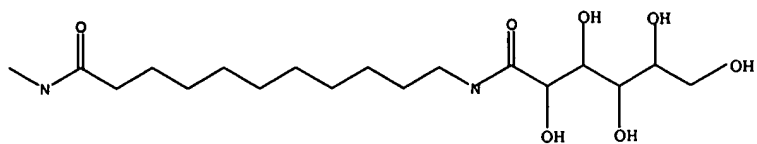
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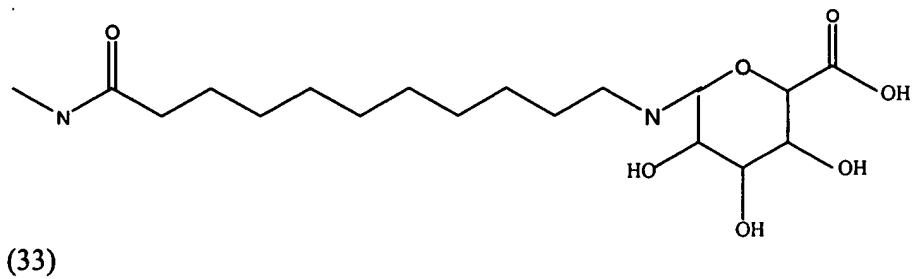
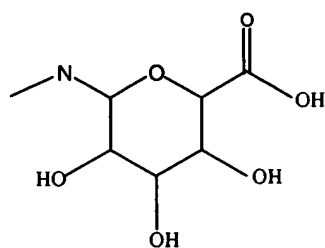
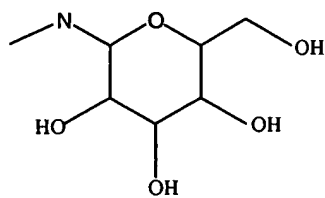
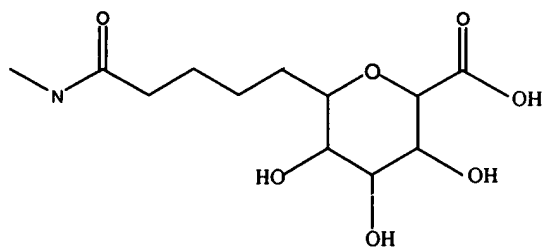
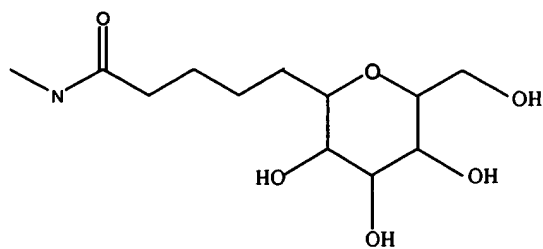
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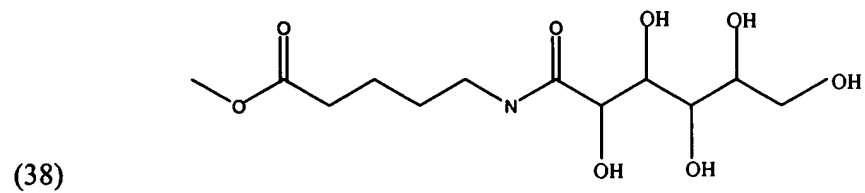
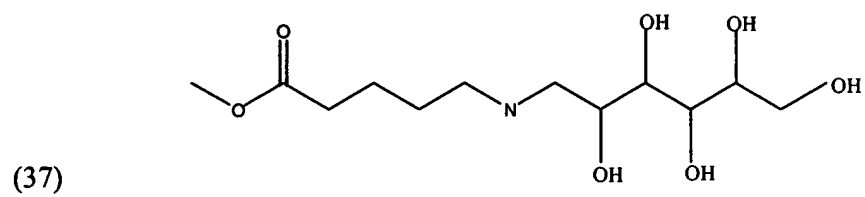
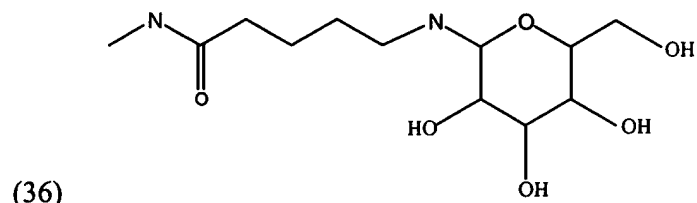
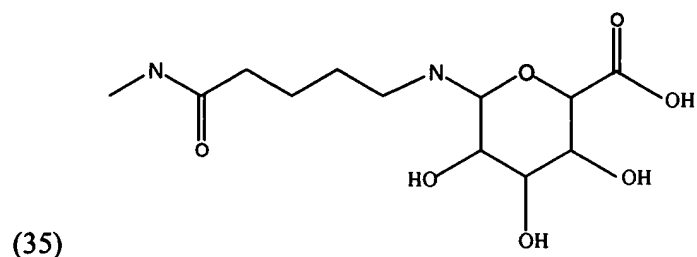
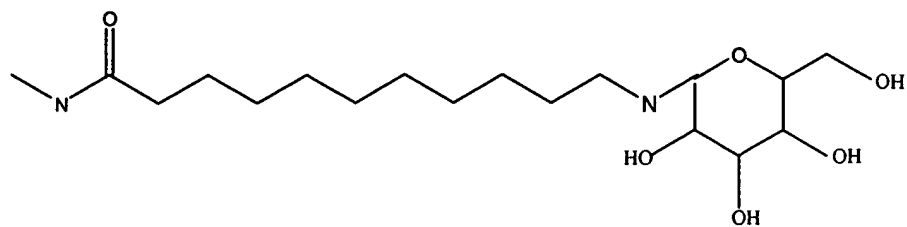


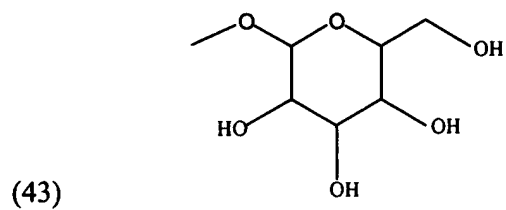
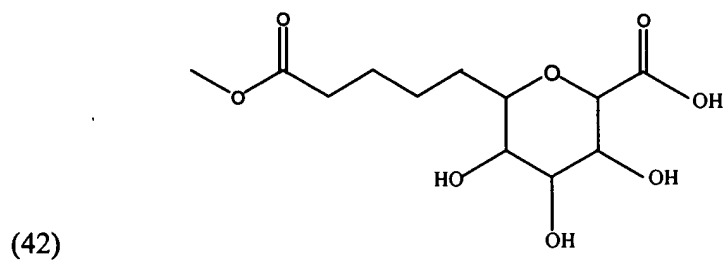
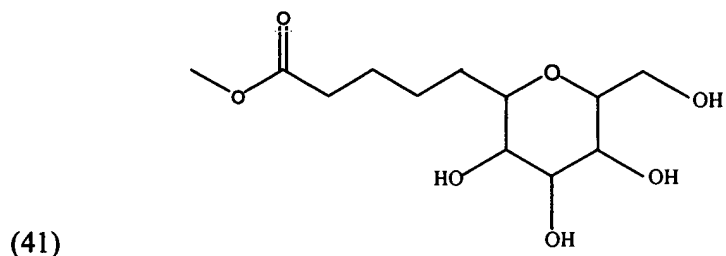
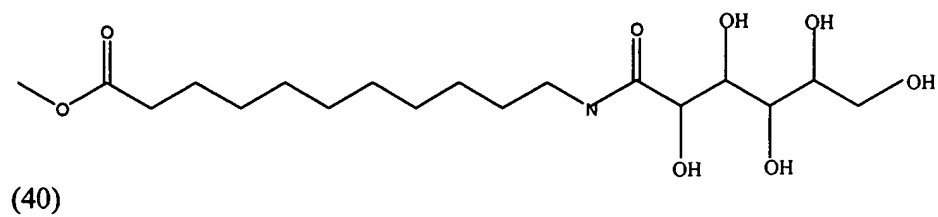
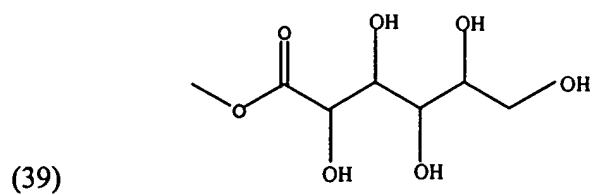
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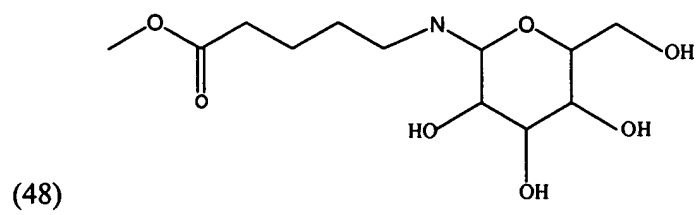
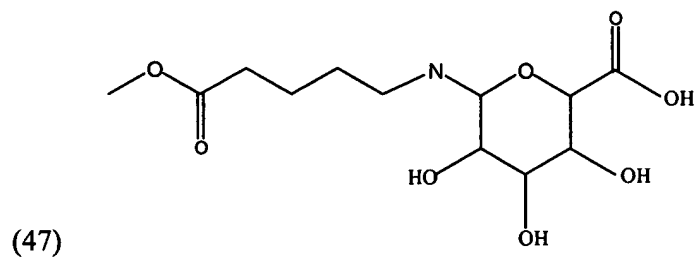
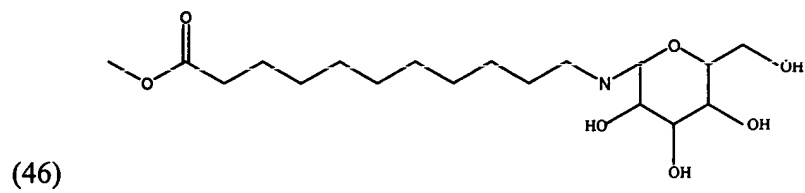
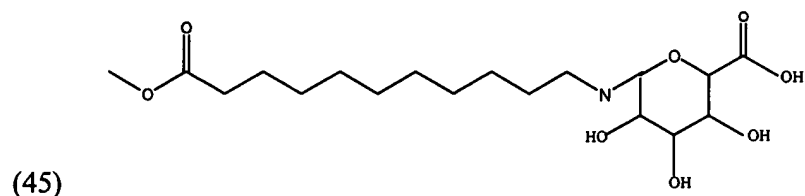
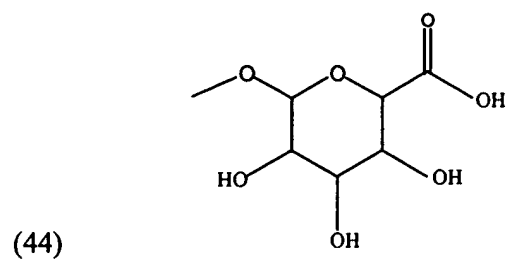


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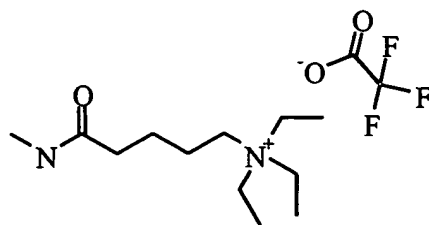




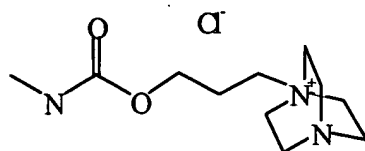




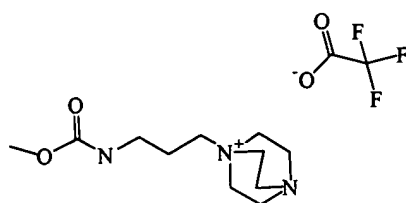
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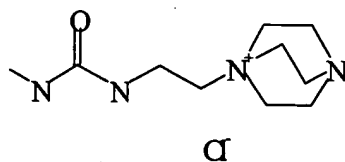
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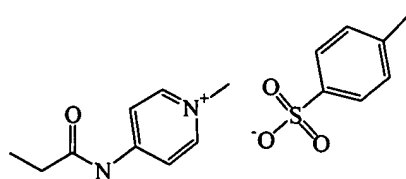
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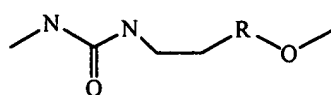
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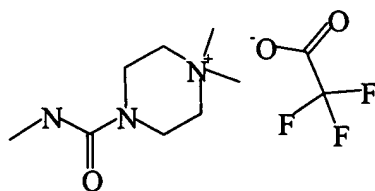
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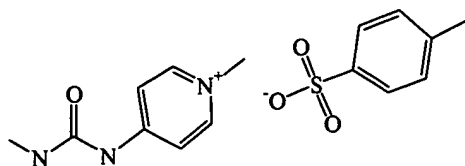
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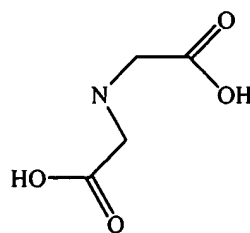
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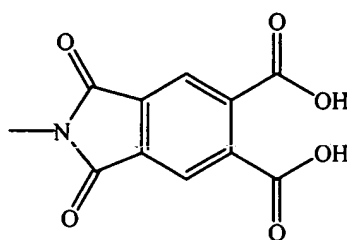
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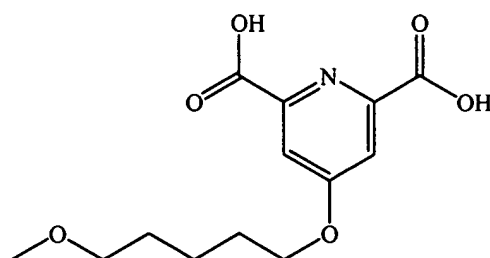
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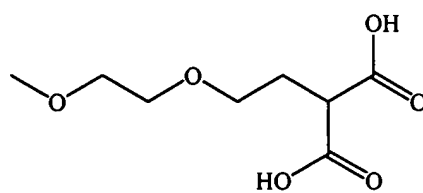
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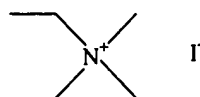
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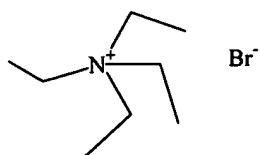
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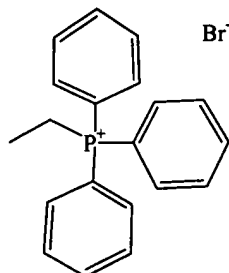
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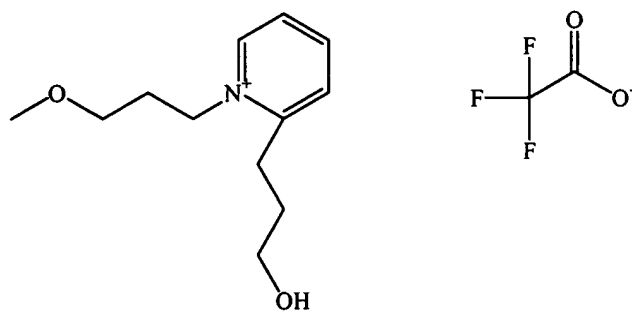
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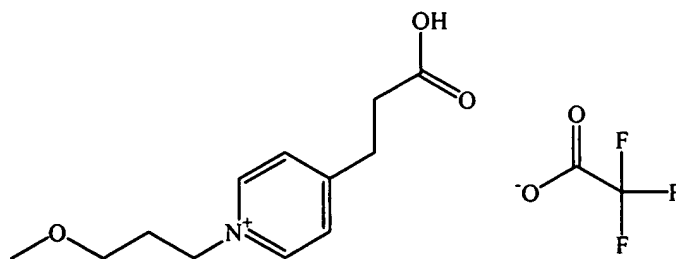
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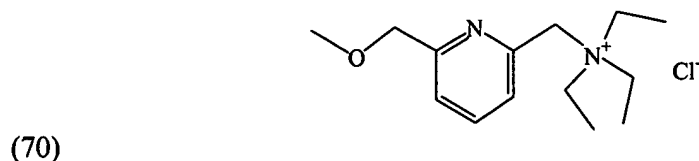
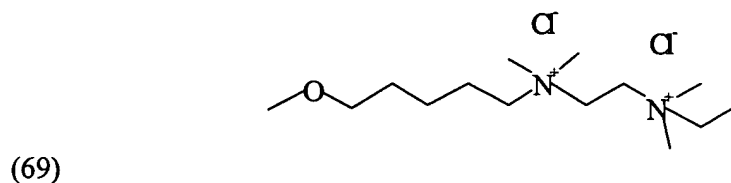
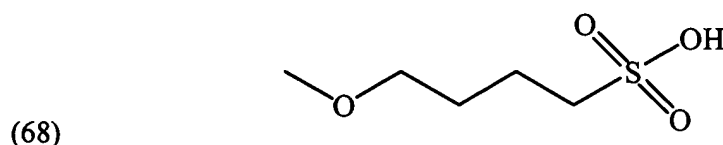
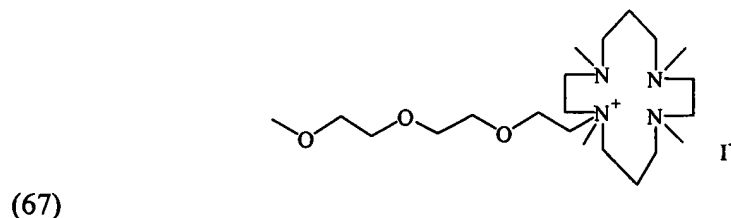
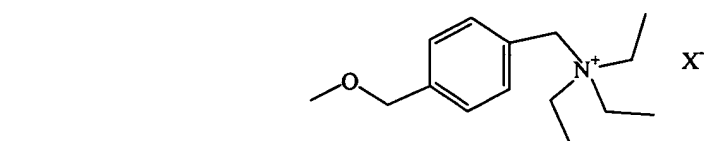


(64)



(65)





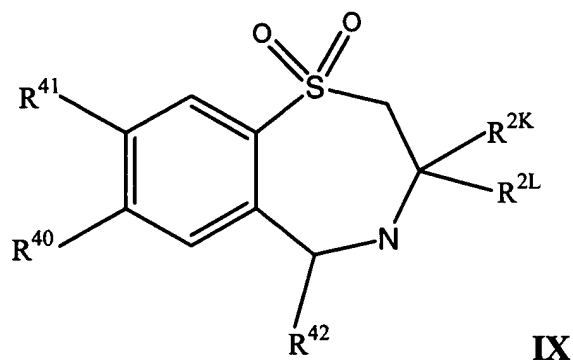
[452] Optionally, R^{38} may be selected from the following: (1) – (24), (25) – (48) or (49) – (70) from Table 5. Further, R^{38} may be acidic or contain a quaternary ammonium nitrogen. Even further, R^{38} may be selected from the following: (1) – (5), (6) – (10), (11) – (15), (16) – (20), (21) – (25), (26) – (30), (31) – (35), (36) – (40), (41) – (45), (46) – (50), (51) – (55), (56) – (60), (61) – (65), (66) – (70), or combinations thereof.

[453] In another embodiment of the compounds of Formula VIII, R^{35} is chloro, and R^{36} is selected from the group consisting of hydroxy and methoxy.

[454] In another embodiment of the compounds of Formula VIII, one of R^{2I} and R^{2J} is ethyl and the other of R^{2I} and R^{2J} is n-butyl; R^{35} is chloro; and R^{36} is hydroxy.

[455] In another embodiment of the compounds of Formula VIII, one of R^{2I} and R^{2J} is ethyl and the other of R^{2I} and R^{2J} is n-butyl; R^{35} is chloro; and R^{36} is methoxy.

[456] Within the compounds of Formula VII is a class of compounds of particular interest corresponding to Formula IX:



[457] wherein:

[458] R^{2K} and R^{2L} are independently selected from C_{1-6} alkyl; and

[459] R^{40} and R^{41} are independently selected from the group consisting of hydrogen, alkoxy, and R^{43} ;

[460] wherein R^{43} is selected from the group consisting of cycloalkyl, aryl and heterocyclyl, wherein said cycloalkyl, aryl and heterocyclyl are substituted with $-N(H)-X-R^{44}$ or $-O-X-R^{44}$ and wherein:

[461] X is selected from the group consisting of:

[462] $-(C=O)_a$ -alkyl-;

[463] $-(C=O)_a$ -alkyl-NH-;

[464] $-(C=O)_a$ -alkyl-O-;

[465] $-(C=O)_a$ -alkyl- $(C=O)_b$; and

[466] a covalent bond; and

[467] R^{44} is selected from selected from the group consisting of monosaccharides, disaccharides, and polysaccharides, wherein said monosaccharides, disaccharides, and polysaccharides may be protected with one or more sugar protecting groups; and

[468] a and b are independently 0 or 1; and

[469] R^{42} is unsubstituted phenyl or R^{43} ; or

[470] a pharmaceutically acceptable salt, solvate, or prodrug thereof;

[471] provided that at least one of R^{40} , R^{41} and R^{42} is R^{43} .

[472] Preferably, R^{43} is phenyl substituted with $-N(H)-X-R^{44}$ or $-O-X-R^{44}$ wherein:

[473] X is selected from the group consisting of:

[474] $-(C=O)_a$ -alkyl-;

[475] $-(C=O)_a$ -alkyl-NH-;

[476] $-(C=O)_a$ -alkyl-O-;

- [477] $-(C=O)_a\text{-alkyl-(C=O)}_b$; and
- [478] a covalent bond; and
- [479] R^{44} is selected from the group consisting of monosaccharides, disaccharides, and polysaccharides; and
- [480] a and b are independently 0 or 1.
- [481] In one embodiment, R^{43} is phenyl substituted at the para-position with $-N(H)\text{-X-}R^{44}$ or $-O\text{-X-}R^{44}$ wherein:
- [482] X is selected from the group consisting of:
- [483] $-(C=O)_a\text{-alkyl-}$;
- [484] $-(C=O)_a\text{-alkyl-NH-}$;
- [485] $-(C=O)_a\text{-alkyl-O-}$;
- [486] $-(C=O)_a\text{-alkyl-(C=O)}_b$; and
- [487] a covalent bond; and
- [488] R^{44} is selected from the group consisting of monosaccharides, disaccharides, and polysaccharides; and
- [489] a and b are independently 0 or 1.
- [490] In another embodiment, R^{43} is phenyl substituted at the meta-position with $-N(H)\text{-X-}R^{44}$ or $-O\text{-X-}R^{44}$ wherein:
- [491] X is selected from the group consisting of:
- [492] $-(C=O)_a\text{-alkyl-}$;
- [493] $-(C=O)_a\text{-alkyl-NH-}$;
- [494] $-(C=O)_a\text{-alkyl-O-}$;

[495] $-(C=O)_a\text{-alkyl-(C=O)}_b$; and

[496] a covalent bond; and

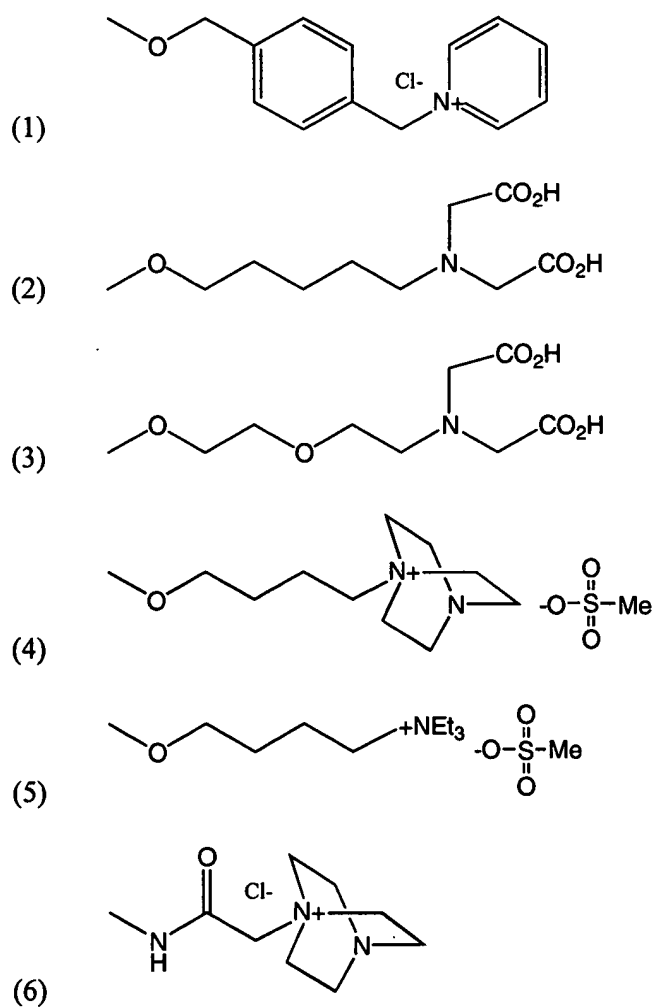
[497] R^{44} is selected from the group consisting of monosaccharides, disaccharides, and polysaccharides; and

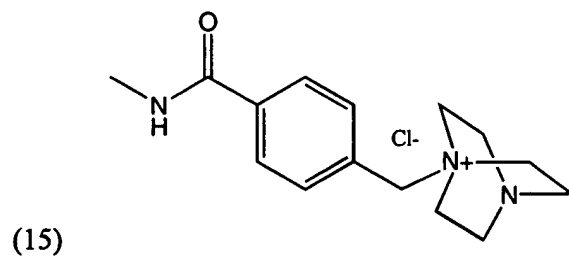
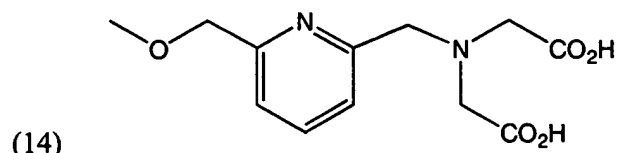
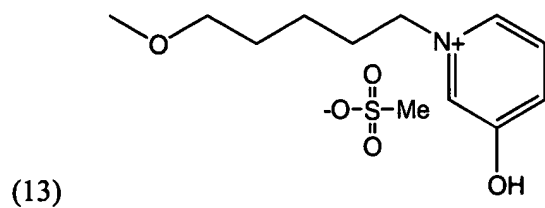
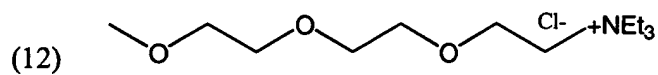
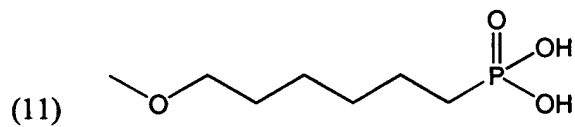
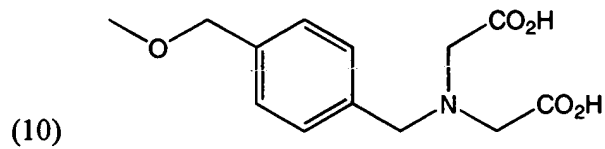
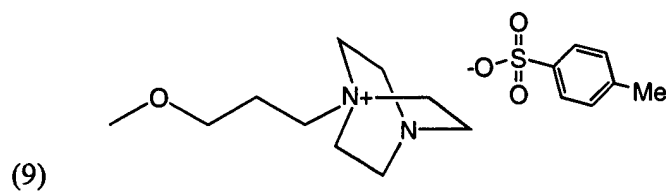
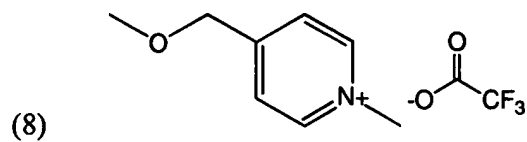
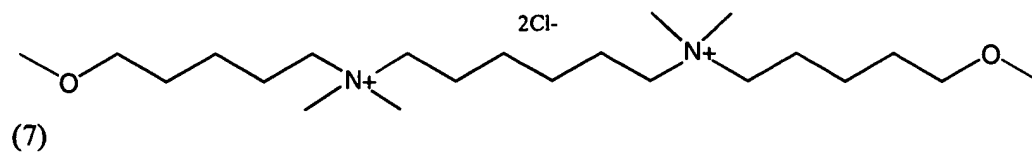
[498] a and b are independently 0 or 1.

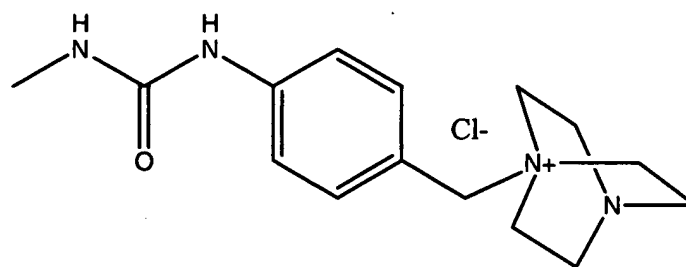
[499] In another embodiment, R^{43} is phenyl substituted with a radical selected from the group consisting of:

TABLE 6

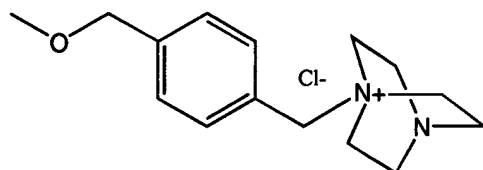
R^{43}



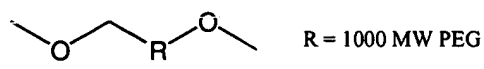




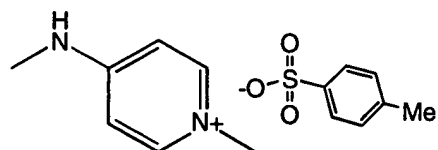
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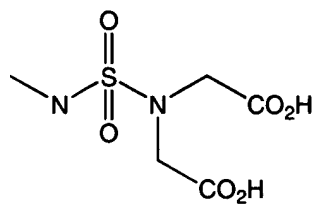
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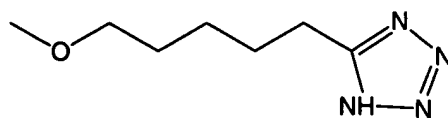
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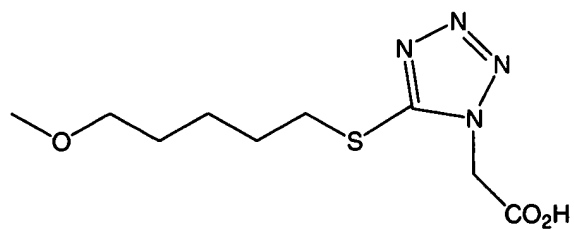
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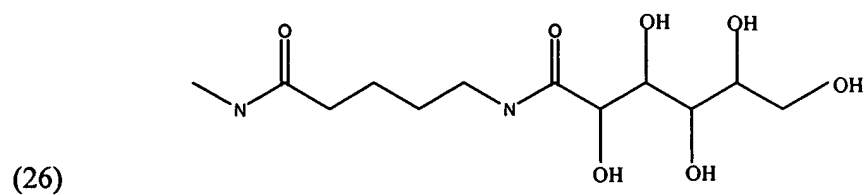
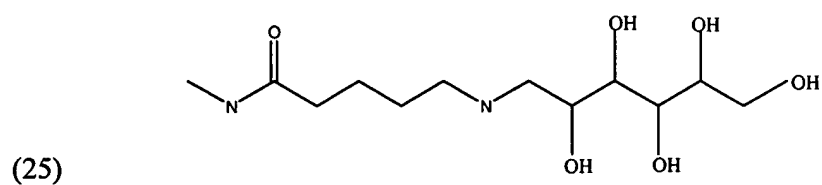
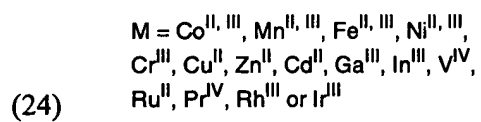
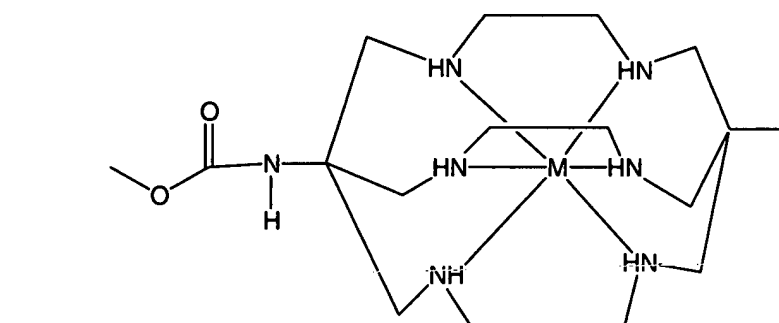
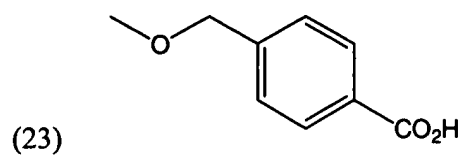
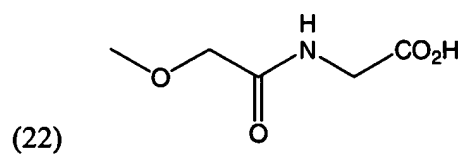


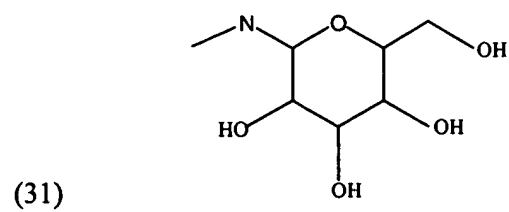
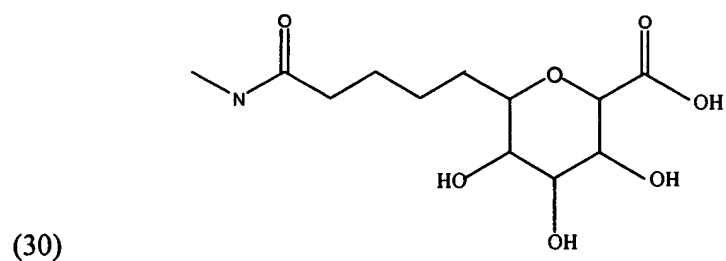
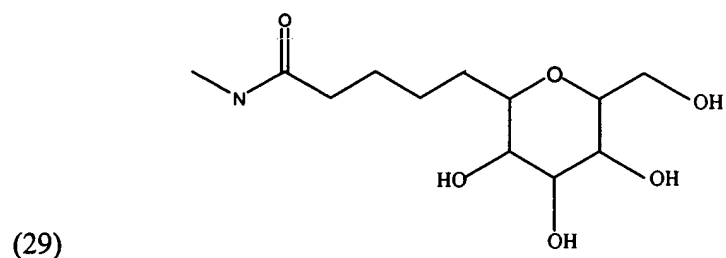
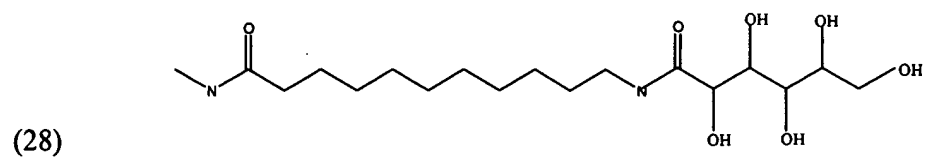
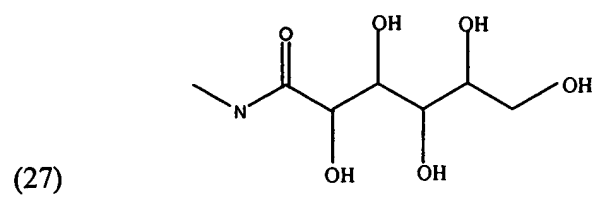
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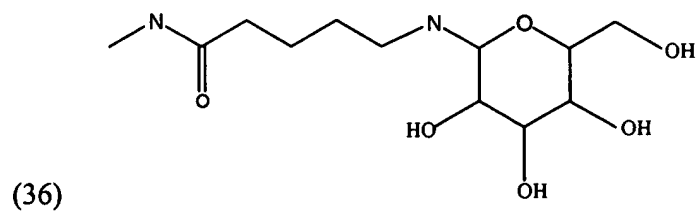
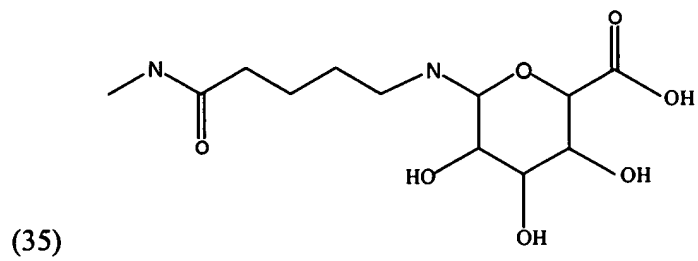
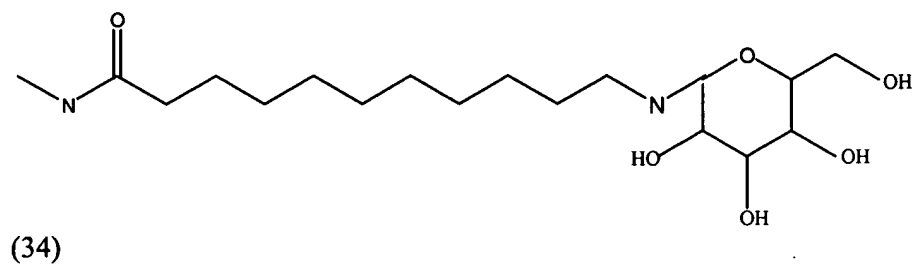
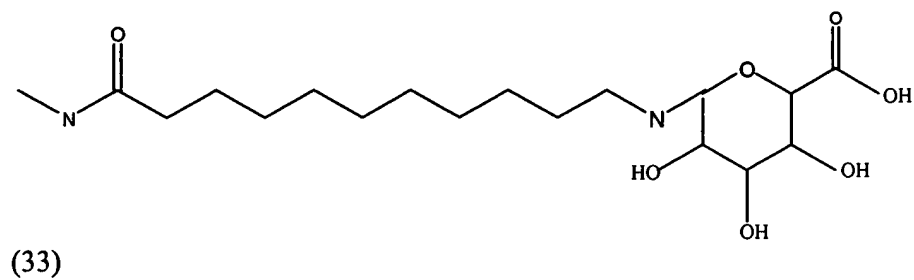
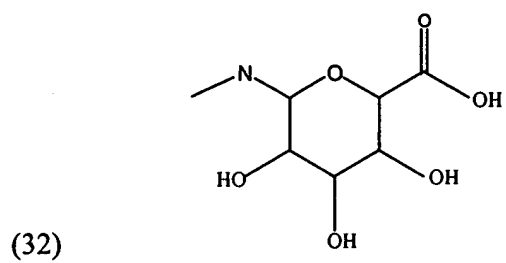


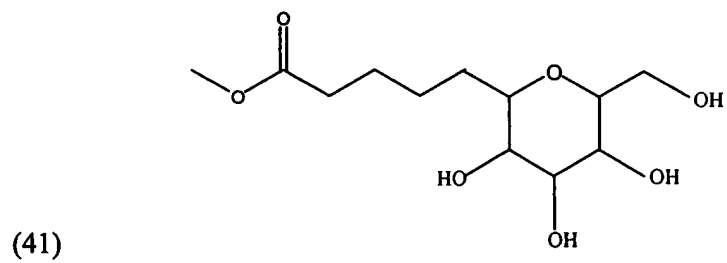
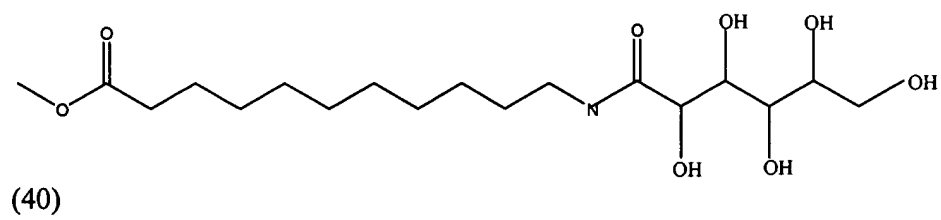
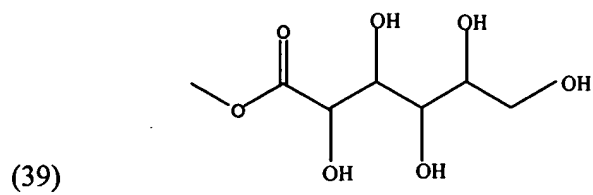
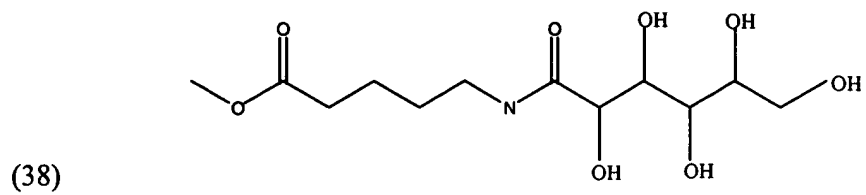
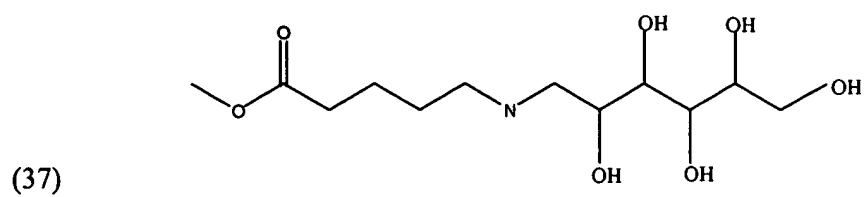
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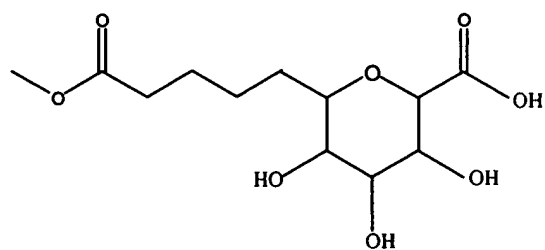
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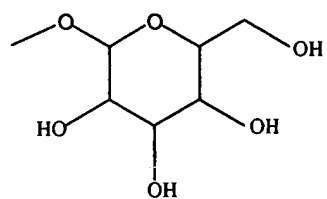




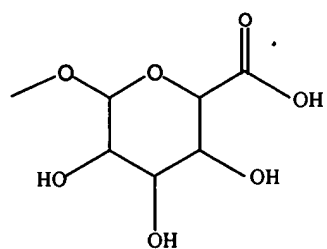




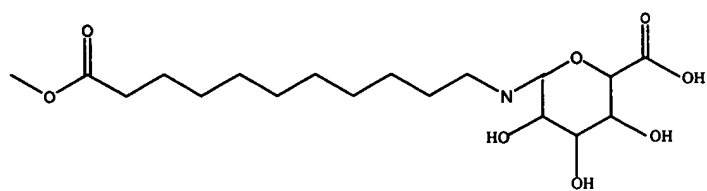
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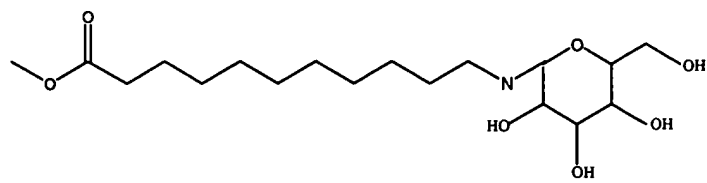
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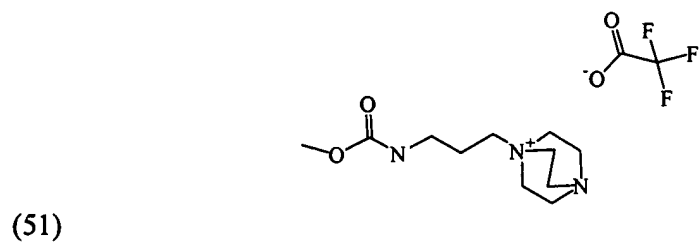
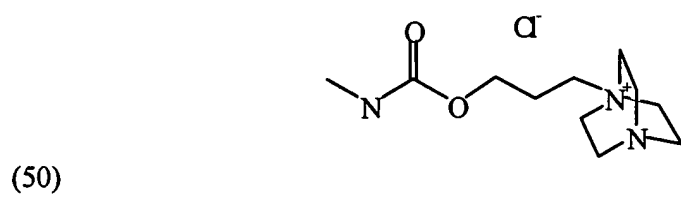
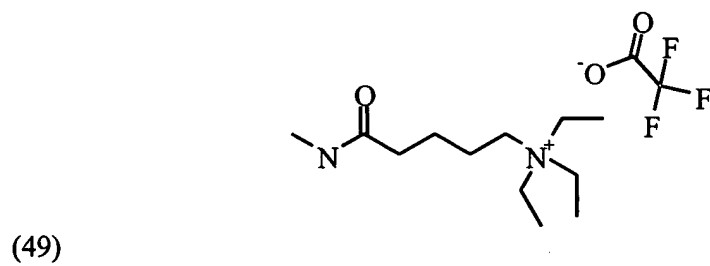
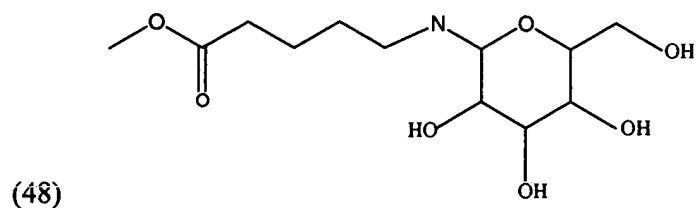
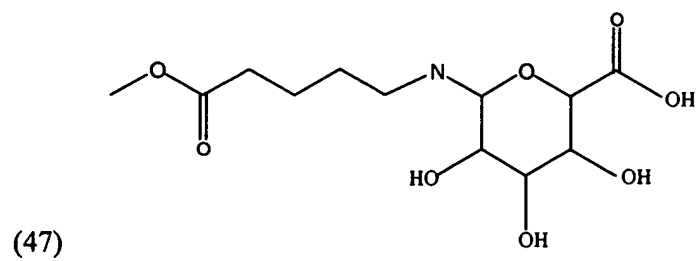
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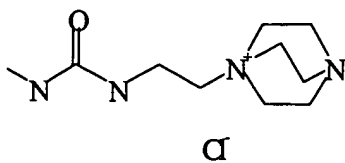


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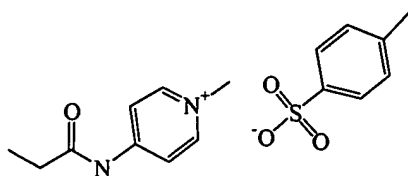


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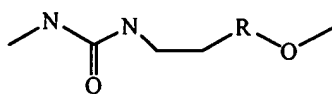




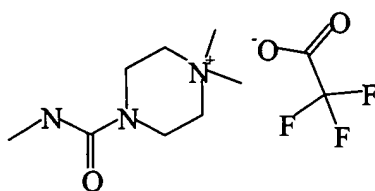
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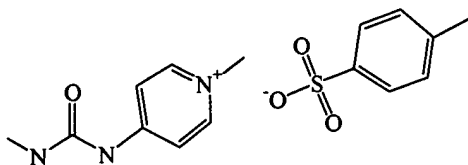
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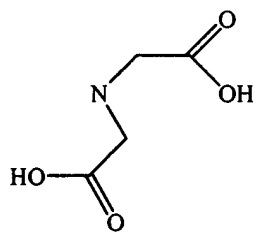
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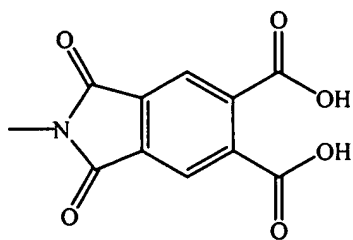
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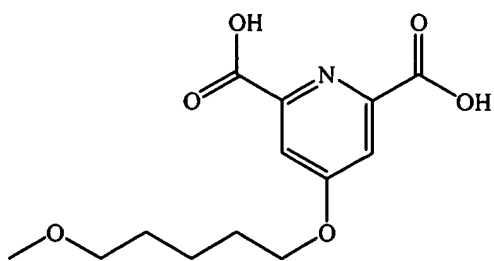


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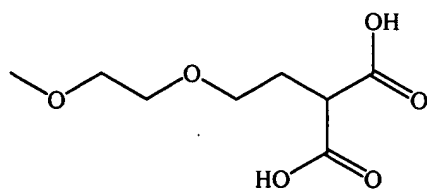


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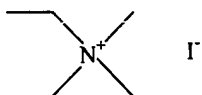
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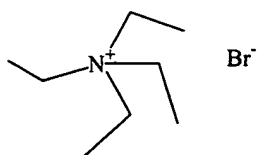
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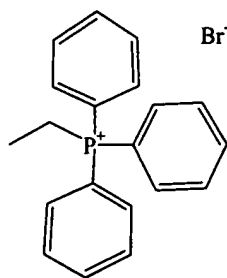
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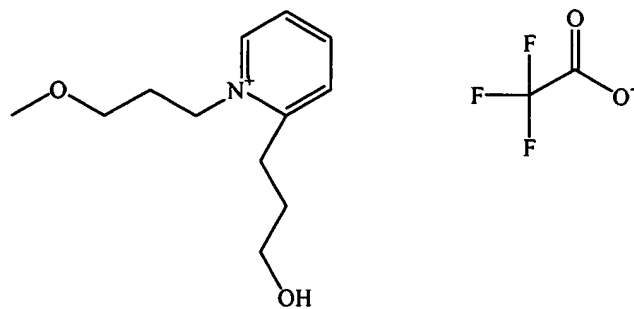
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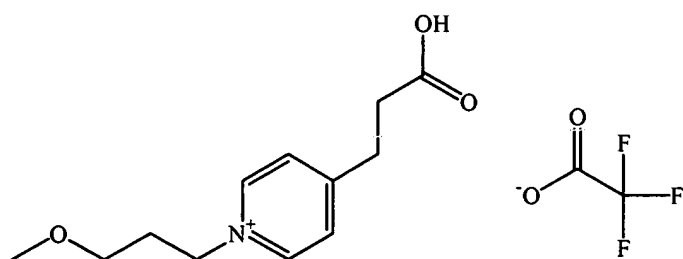
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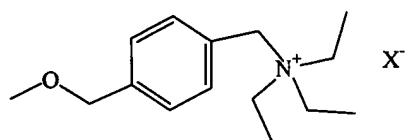
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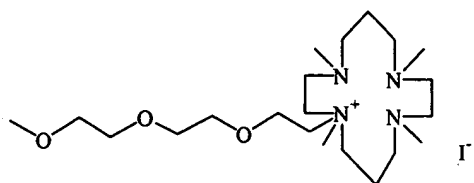
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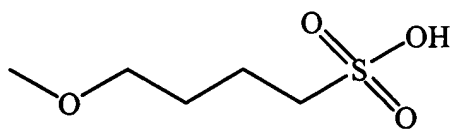
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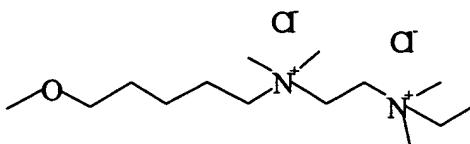


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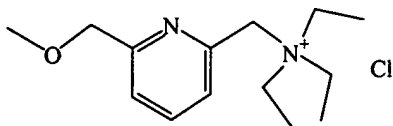


(68)





(69)



(70)

[500] Optionally, R^{43} may be selected from the following: (1) – (24), (25) – (48) or (49) – (70) from Table 6. Further, R^{43} may be acidic or contain a quaternary ammonium nitrogen. Even further, R^{43} may be selected from the following: (1) – (5), (6) – (10), (11) – (15), (16) – (20), (21) – (25), (26) – (30), (31) – (35), (36) – (40), (41) – (45), (46) – (50), (51) – (55), (56) – (60), (61) – (65), (66) – (70), or combinations thereof. In another embodiment of the compounds of Formula IX, R^{40} and R^{41} are independently selected from hydrogen and methoxy.

[501] In another embodiment of the compounds of Formula IX, one of R^{2K} and R^{2L} is ethyl and the other of R^{2K} and R^{2L} is n-butyl; and R^{40} and R^{41} are hydrogen.

[502] In another embodiment of the compounds of Formula IX, one of R^{2K} and R^{2L} is ethyl and the other of R^{2K} and R^{2L} is n-butyl; and R^{40} and R^{41} are methoxy.

[503] In each of the various embodiments of the invention described above, at least one or more of the following conditions preferably are satisfied:

[504] (1) j is 1 or 2. Preferably, j is 2; and/or

[505] (2) The substituents at the 2-position of the benzothiazepine are independently selected from the group consisting of hydrogen and alkyl. Preferably, these substituents are hydrogen; and/or

[506] (3) The substituents at the 3-position of the benzothiazepine are independently selected from the group consisting of hydrogen and alkyl. Preferably, these substituents are independently selected from the group consisting of C_{1-6} alkyl. More preferably, these

substituents are selected from the group consisting of ethyl, propyl and butyl. Still more preferably, either (a) one of these substituents is ethyl and the other of these substituents is n-butyl, or (b) both of these substituents are n-butyl; and/or

- [507] (4) The 4-position nitrogen substituent (*e.g.*, R^3 , when the compound is a 1,4-benzothiazepine) or one or both the 4-position carbon substituents (*e.g.*, one or two R^4 group(s) at the 4-position carbon, when the compound is a 1,5-benzothiazepine) of the benzothiazepine are independently selected from the group consisting of hydrogen and hydroxy; and/or
- [508] (5) The 5-position nitrogen substituent (*e.g.*, R^3 , when the compound is a 1,5-benzothiazepine) or one of the 5-position carbon substituents (*e.g.*, R^4 , when the compound is a 1,4-benzothiazepine) of the benzothiazepine is substituted aryl wherein said aryl is substituted with (a) a moiety possessing an overall positive charge; and/or (b) a moiety comprising a quaternary ammonium group or a quaternary amine salt; and/or (c) a moiety comprising a phosphonic acid group or at least two carboxyl groups. Preferably, this substituent is substituted phenyl. More preferably, this substituent is phenyl that is glucuronidated or monosubstituted with a radical selected from the group consisting of $-OR^{13}$, $-NR^{13}C(O)R^{14}$, $-NR^{13}C(O)NR^{14}R^{15}$, $-NR^{13}CO_2R^{14}$, $-OC(O)R^{13}$, $-OC(O)NR^{13}R^{14}$, $-NR^{13}SOR^{14}$, $-NR^{13}SO_2R^{14}$, $-NR^{13}SONR^{14}R^{15}$, and $-NR^{13}SO_2NR^{14}R^{15}$ wherein R^{13} , R^{14} and R^{15} are as previously defined for compounds of Formula I. Still more preferably, this substituent is phenyl that is monosubstituted with a radical selected from the group consisting of $-OR^{13}$ and $-NR^{13}SO_2NR^{14}R^{15}$. Still more preferably, this substituent is phenyl substituted at the para or meta position with $-OR^{13}$ or $-NR^{13}SO_2NR^{14}R^{15}$ wherein R^{13} comprises a quaternary heterocycle, quaternary heteroaryl, carboxy or substituted amino; and/or
- [509] (6) When the compound is a 1,4-benzothiazepine, the other substituent at the 5-position carbon of the benzothiazepine is hydrogen; and/or
- [510] (7) One or more substituents of the benzo ring of the benzothiazepine are independently selected from the group consisting of halogen, $-OR^{13}$ and $-NR^{13}R^{14}$, wherein $R^{13}R^{14}$ are as previously defined for compounds of Formula I. Preferably, the substituents of the benzo ring are independently selected from the group consisting of halogen, hydroxy,

alkoxy, amino, alkylamino and dialkylamino. Still more preferably, the substituents are independently selected from the group consisting of chloro, methoxy and dimethylamino.

[511] Alternative Forms of Novel Compounds

[512] Also included in the family of compounds of Formulae I, IA, IB, III, V, VII, VIII and IX are (1) the stereoisomers thereof, (b) the pharmaceutically-acceptable salts thereof, (c) the tautomers thereof, (d) the protected acids and the conjugate acids thereof, and (e) the prodrugs thereof.

[513] The stereoisomers of these compounds may include, but are not limited to, enantiomers, diastereomers, racemic mixtures and other mixtures thereof. Such stereoisomers can be prepared and separated using conventional techniques, either by reacting enantiomeric starting materials, or by separating isomers of compounds of the present invention. Isomers may include geometric isomers, for example cis isomers or trans isomers across a double bond. All such isomers are contemplated among the compounds of the present invention. Such isomers may be used in either pure form or in admixture with those inhibitors described above.

[514] The protected acids of these compounds include, but are not limited to, protected acids such as esters, hydroxyamino derivatives, amides and sulfonamides. Thus, for example, primary and secondary amines can be reacted with carboxylic acid substituted forms of the compounds of Formulae I, IA, IB, III, V, VII, VIII and IX to form amides which can be useful as prodrugs. Preferred amines are heterocyclicamines, including optionally substituted aminothiazoles, optionally substituted amino-isoxazoles, optionally substituted aminopyridines, optionally substituted aniline derivatives, optionally substituted sulfonamides, optionally substituted aminocarboxylic acids, and the like. The esters, hydroxyamino derivatives and sulfonamides can be prepared from the acids by methods known to one skilled in the art.

[515] Pharmaceutically-acceptable salts include salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not

critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formulae I, IA, IB, III, V, VII, VIII and IX may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, salicylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, algenic, N-hydroxybutyric, salicylic, galactaric and galacturonic acid.

[516] Suitable pharmaceutically-acceptable base addition salts of compounds of Formulae I, IA, IB, III, V, VII, VIII and IX include metallic salts, such as salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc, or salts made from organic bases including primary, secondary and tertiary amines, substituted amines including cyclic amines, such as caffeine, arginine, diethylamine, N-ethyl piperidine, histidine, glucamine, isopropylamine, lysine, morpholine, N-ethyl morpholine, piperazine, piperidine, triethylamine, trimethylamine. The above salts may be prepared by conventional means from the corresponding compounds of the invention by reacting, for example, the appropriate acid or base with the compounds of Formulae I, IA, IB, III, V, VII, VIII and IX.

[517] Dosages and Treatment Regimen

[518] Dosage levels of the compounds of Formulae I, IA, IB, III, V, VII, VIII and IX typically are on the order of about 0.001 mg to about 10,000 mg daily, with preferred levels of about 0.005 mg to about 1,000 mg daily, more preferred levels of about 0.008 to about 100 mg daily, and still more preferred levels of about 0.05 mg to about 50 mg daily.

- [519] The dosage regimen to prevent, treat, give relief from, or ameliorate a hyperlipidemic condition or disorder, or to otherwise protect against or treat further high cholesterol plasma or blood levels with the combinations and compositions of the present invention is selected in accordance with a variety of factors. These factors include the type, age, weight, sex, diet, and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular inhibitors employed, whether a drug delivery system is utilized, and whether the inhibitors are administered with other active ingredients. Thus, the dosage regimen actually employed may vary widely and therefore deviate from the preferred dosage regimen set forth above.
- [520] Initial treatment of a patient suffering from a hyperlipidemic condition or disorder can begin with the dosages indicated above. Treatment generally should be continued as necessary over a period of several weeks to several months or years until the hyperlipidemic condition or disorder has been controlled or eliminated. Patients undergoing treatment with the combinations or compositions disclosed herein can be routinely monitored, for example, by measuring serum LDL and total cholesterol levels by any of the methods well-known in the art, to determine the effectiveness of the combination therapy. Continuous analysis of such data permits modification of the treatment regimen during therapy so that optimal effective amounts of each type of inhibitor are administered at any time, and so that the duration of treatment can be determined as well. In this way, the treatment regimen/dosing schedule can be rationally modified over the course of therapy so that the lowest amount of inhibitor that exhibits satisfactory effectiveness is administered, and so that administration is continued only so long as is necessary to successfully treat the hyperlipidemic condition.
- [521] The total daily dose of each drug can be administered to the patient in a single dose, or in proportionate multiple subdoses. Subdoses can be administered two to six times per day. Doses can be in immediate release form or sustained release form effective to obtain desired results.

[522] Pharmaceutical Compositions

[523] For the prophylaxis or treatment of the conditions and disorders referred to above, the compound can be administered as the compound *per se*. Alternatively, pharmaceutically-acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent compound.

[524] The compounds of the present invention also can be presented with an acceptable carrier in the form of a pharmaceutical composition. The carrier must be acceptable in the sense of being compatible with the other ingredients of the composition and must not be deleterious to the recipient. The carrier can be a solid or a liquid, or both, and preferably is formulated with the compound as a unit-dose composition, for example, a tablet, which can contain from 0.05% to 95% by weight of the active compounds. Other pharmacologically active substances can also be present, including other compounds useful in the treatment of a hyperlipidemic condition.

[525] The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The active compounds and compositions, for example, may be administered orally, pulmonarily, mucosally, intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically. Unit dose formulations, particularly orally administrable unit dose formulations such as tablets or capsules, generally contain, for example, from about 0.001 to about 500 mg, preferably about 0.005 mg to about 100 mg, and more preferably from about 0.01 to about 50 mg, of the active ingredient. In the case of pharmaceutically acceptable salts, the weights indicated above for the active ingredient refer to the weight of the pharmaceutically active ion derived from the salt.

[526] For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. If administered *per os*, the compounds may be admixed with, for example, lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc,

stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration.

[527] Oral delivery of the compounds of the present invention can include formulations, as are well known in the art, to provide immediate delivery or prolonged or sustained delivery of the drug to the gastrointestinal tract by any number of mechanisms. Immediate delivery formulations include, but are not limited to, oral solutions, oral suspensions, fast-dissolving tablets or capsules, disintegrating tablets and the like. Prolonged or sustained delivery formulations include, but are not limited to, pH sensitive release from the dosage form based on the changing pH of the small intestine, slow erosion of a tablet or capsule, retention in the stomach based on the physical properties of the formulation, bioadhesion of the dosage form to the mucosal lining of the intestinal tract, or enzymatic release of the active drug from the dosage form. The intended effect is to extend the time period over which the active drug molecule is delivered to the site of action (for example, the ileum for the ASBT inhibitor) by manipulation of the dosage form. Thus, enteric-coated and enteric--coated controlled release formulations are within the scope of the present invention. Suitable enteric coatings include cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethyl-cellulose phthalate and anionic polymers of methacrylic acid and methacrylic acid methyl ester. Such prolonged or sustained delivery formulations preferably are in dispersed form at the time they reach the ileum.

[528] Pharmaceutical compositions suitable for oral administration can be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of at least one compound of the present invention; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. As indicated, such compositions can be prepared by any suitable method of pharmacy which includes the step of bringing into association the inhibitor(s) and the carrier (which can constitute one or more accessory ingredients). In general, the compositions are prepared by uniformly and

intimately admixing the inhibitor(s) with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet can be prepared by compressing or molding a powder or granules of the inhibitors, optionally with one or more assessor ingredients. Compressed tablets can be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Molded tablets can be made, for example, by molding the powdered compound in a suitable machine.

- [529] Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.
- [530] Pharmaceutical compositions suitable for buccal (sub-lingual) administration include lozenges comprising a compound of the present invention in a flavored base, usually sucrose, and acacia or tragacanth, and pastilles comprising the inhibitors in an inert base such as gelatin and glycerin or sucrose and acacia.
- [531] Formulations for parenteral administration, for example, may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.
- [532] Pharmaceutically acceptable carriers encompass all the foregoing and the like. The pharmaceutical compositions of the invention can be prepared by any of the well-known techniques of pharmacy, such as admixing the components. The above considerations in regard to effective formulations and administration procedures are well known in the art and are described in standard textbooks. Formulation of drugs

is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania, 1975; Liberman, et al., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Kibbe, et al., Eds., Handbook of Pharmaceutical Excipients (3rd Ed.), American Pharmaceutical Association, Washington, 1999.

[533] Methods of Use

[534] The present invention also includes methods for the treatment of a hyperlipidemic condition or conditions in a subject, including the prophylactic or preventative treatment of a hyperlipidemic condition or conditions in a subject, comprising administering to a subject, particularly a subject in need thereof, a therapeutically effective amount of a compound of Formulae I, IA, IB, III, V, VII, VIII or IX.

[535] The present invention further includes methods for the treatment of gallstones in a subject, including the prophylactic or preventative treatment of a hyperlipidemic condition or conditions in a subject, comprising administering to a subject, particularly a subject in need thereof, a therapeutically effective amount of a compound of Formulae I, IA, IB, III, V, VII, VIII or IX.

[536] The methods and compounds of the present invention may be used alone or in conjunction with additional therapies and/or compounds known to those skilled in the art in the prevention or treatment of hyperlipidemia. Alternatively, the methods and compounds described herein may be used, partially or completely, in conjunctive therapy. By way of example, the compounds may be administered alone or in conjunction with other anti-hyperlipidemic agents, such as together with HMG-Co-A reductase inhibitors, bile acid sequestering agents, fibric acid derivatives, nicotinic acid, and/or probucol.

[537] Definitions

[538] The term "subject" as used herein includes an animal, preferably a mammal, and particularly a human, who has been the object of treatment, observation or experiment.

- [539] The term "treatment" includes any process, action, application, therapy, or the like, wherein a subject is subject to medical aid with the object of improving the subject's condition, directly or indirectly.
- [540] The terms "prophylaxis" and "prevention" include either preventing the onset of a clinically evident hyperlipidemic condition or disorder altogether or preventing the onset of a preclinically evident stage of a hyperlipidemic condition or disorder in individuals. These terms encompass the prophylactic treatment of a subject at risk of developing a hyperlipidemic condition or disorder such as, but not limited to, atherosclerosis and hypercholesterolemia.
- [541] The term "combination therapy" or "co-therapy" means the administration of two or more therapeutic agents to treat a hyperlipidemic condition and/or disorder, for example atherosclerosis and hypercholesterolemia. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each inhibitor agent. In addition, such administration encompasses use of each type of therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the hyperlipidemic condition.
- [542] The phrase "therapeutically-effective" qualifies the amount of each agent that will achieve the goal of improvement in hyperlipidemic condition or disorder severity and the frequency of incidence over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies.
- [543] The term "pharmaceutically acceptable" is used adjectivally herein to mean that the modified noun is appropriate for use in a pharmaceutical product. Pharmaceutically acceptable cations, for example, include metallic ions and organic ions. More preferred metallic ions include, but are not limited to appropriate alkali metal salts, alkaline earth metal salts and other physiologically acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N,N'-

dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include without limitation hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid, oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

[544] The term “prodrug” includes a compound that is a drug precursor that, following administration to a subject and subsequent absorption, is converted to an active species *in vivo* via some process, such as metabolic conversion. Other products from the conversion process are easily disposed of by the body. More preferred prodrugs produce products from the conversion process that are generally accepted as safe. For example, the prodrug may be an acylated form of the active compound.

[545] The term "ASBT inhibitor" includes a compound capable of inhibiting absorption of bile acids from the intestine into the circulatory system of a mammal, such as a human. This includes increasing the fecal excretion of bile acids, as well as reducing the blood plasma or serum concentrations of cholesterol and cholesterol ester, and more specifically, reducing LDL and VLDL cholesterol. Conditions or diseases which benefit from the prophylaxis or treatment by bile acid transport inhibition include, for example, a hyperlipidemic condition such as atherosclerosis.

[546] Where the term “alkyl” is used, either alone or within other terms such as “haloalkyl”, and “hydroxyalkyl”, it includes linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are “lower alkyl” radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like. Even more preferred are lower alkyl radicals having one to three carbon atoms.

[547] Where the term “alkenyl” is used, either alone or within other terms such as “arylalkenyl”, it includes linear or branched radicals having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, two to about

twelve carbon atoms. More preferred alkenyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl.

[548] The terms "alkenyl" and "lower alkenyl", include radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

[549] The term "alkynyl" includes linear or branched radicals having two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about ten carbon atoms. Most preferred are lower alkynyl radicals having two to about six carbon atoms. Examples of such radicals include propargyl, butynyl, and the like.

[550] The term "cycloalkyl" includes saturated carbocyclic radicals having three to about twelve carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to about ten carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "cycloalkyl" additionally encompasses spiro systems wherein the cycloalkyl ring has a carbon ring atom in common with the seven-membered heterocyclic ring of the benzothiazepine.

[551] The term "cycloalkenyl" includes partially unsaturated carbocyclic radicals having three to twelve carbon atoms. Cycloalkenyl radicals that are partially unsaturated carbocyclic radicals that contain two double bonds (that may or may not be conjugated) can be called "cycloalkyldienyl". More preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having four to about ten carbon atoms. Examples of such radicals include cyclobutenyl, cyclopentenyl and cyclohexenyl.

[552] The term "halo" and "halogen" includes halogens such as fluorine, chlorine, bromine or iodine atoms. The term "haloalkyl" includes radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower

haloalkyl” includes radicals having one to six carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. “Perfluoroalkyl” includes alkyl radicals having all hydrogen atoms replaced with fluoro atoms. Examples include trifluoromethyl and pentafluoroethyl.

- [553] The term “hydroxyalkyl” includes linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are “lower hydroxyalkyl” radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. Even more preferred are lower hydroxyalkyl radicals having one to three carbon atoms.
- [554] The term “aryl”, alone or in combination, includes a carbocyclic aromatic system containing one or more rings wherein such rings may be attached together in a pendent manner or may be fused. The term “aryl” includes aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane, biphenyl, and anthracenyl. More preferred aryl is phenyl. Said “aryl” group may have one to three substituents such as lower alkyl, hydroxy, halo, haloalkyl, nitro, cyano, alkoxy and lower alkylamino.
- [555] The term “heterocyclyl” includes saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Preferred heterocyclyl are 3-10 membered ring heterocyclyl, particularly 5-8 membered ring heterocyclyl. Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl]; saturated 3 to 6-membered heteromonocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl]; saturated 3 to 6-membered heteromonocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl]. Examples of partially saturated heterocyclyl

radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals, include unsaturated 5 to 6 membered heteromonocyclyl groups containing 1 to 4 nitrogen atoms, for example, pyrrolinyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl]; unsaturated condensed heterocyclic groups containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl]; unsaturated 3 to 6-membered heteromonocyclic groups containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic groups containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl]; unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl]; unsaturated 5 to 6-membered heteromonocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl]; unsaturated condensed heterocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl] and the like. The term also includes radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclyl" group may have 1 to 3 substituents such as lower alkyl, hydroxy, oxo, amino and lower alkylamino.

- [556] Heterocyclic radicals can include fused or unfused radicals, particularly 3-10 membered fused or unfused radicals. Preferred examples of heteroaryl radicals include benzofuryl, 2,3-dihydrobenzofuryl, benzothienyl, indolyl, dihydroindolyl, chromanyl, benzopyran, thiochromanyl, benzothiopyran, benzodioxolyl, benzodioxanyl, pyridyl, thienyl, thiazolyl, furyl, and pyrazinyl. More preferred heteroaryl radicals are 5- or 6-membered heteroaryl, containing one or two heteroatoms selected from sulfur nitrogen and oxygen, selected from thienyl, furanyl,

thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, piperidinyl and pyrazinyl.

- [557] The term "heteroaryl" includes a fully unsaturated heterocyclyl.
- [558] In either "heterocyclyl" or "heteroaryl," the point of attachment to the molecule of interest can be at the heteroatom or elsewhere within the ring.
- [559] The term "triazolyl" includes all positional isomers. In all other heterocyclyl and heteroaryl which contain more than one ring heteroatom and for which isomers are possible, such isomers are included in the definition of said heterocyclyl and heteroaryl.
- [560] The term "quaternary heterocyclyl" includes a heterocyclyl in which one or more of the heteroatoms, for example, nitrogen, sulfur, phosphorus or oxygen, has such a number of bonds that it is positively charged (and therefore the term is intended to encompass both ternary and quaternary positively charged structures). The point of attachment of the quaternary heterocyclyl to the molecule of interest can be at a heteroatom or elsewhere.
- [561] The term "quaternary heteroaryl" includes a heteroaryl in which one or more of the heteroatoms, for example, nitrogen, sulfur, phosphorus or oxygen, has such a number of bonds that it is positively charged (and therefore the term is intended to encompass both ternary and quaternary positively charged structures). The point of attachment of the quaternary heteroaryl to the molecule of interest can be at a heteroatom or elsewhere.
- [562] The term "oxo" includes a doubly bonded oxygen.
- [563] The term "polyalkyl" includes a branched or straight hydrocarbon chain having a molecular weight up to about 20,000, more preferably up to about 10,000, and most preferably up to about 5,000.
- [564] The term "polyether" includes a polyalkyl wherein one or more carbons are replaced by oxygen, wherein the polyether has a molecular weight up to about 20,000, more preferably up to about 10,000, and most preferably up to about 5,000.

- [565] The term "polyalkoxy" includes a polymer of alkylene oxides, wherein the polyalkoxy has a molecular weight up to about 20,000, more preferably up to about 10,000, and most preferably up to about 5,000.
- [566] The term "carbohydrate residue" encompasses residues derived from carbohydrates such as, but is not limited to, mono-, di-, tri-, tetra- and polysaccharides wherein the polysaccharides can have a molecular weight of up to about 20,000, for example, hydroxypropyl-methylcellulose or chitosan residue; compounds derived from aldoses and ketoses with 3 to 7 carbon atoms and which belong to the D- or L-series; aminosugars; sugar alcohols; and saccharic acids. Nonlimiting specific examples of such carbohydrates include glucose, mannose, fructose, galactose, ribose, erythrose, glyceraldehyde, sedoheptulose, glucosamine, galactosamine, glucuronic acid, galacturonic acid, gluconic acid, galactonic acid, mannoic acid, glucamine, 3-amino-1,2-propanediol, glucaric acid and galactaric acid.
- [567] The term "peptide residue" includes polyamino acid residue containing up to about 100 amino acid units.
- [568] The term "polypeptide residue" includes a polyamino acid residue containing from about 100 amino acid units to about 1000 amino acid units, more preferably from about 100 amino acid units to about 750 amino acid units, and most preferably from about 100 amino acid units to about 500 amino acid units.
- [569] The term "alkylammoniumalkyl" includes an -NH_2 group or a mono-, di- or tri-substituted amino group, any of which is bonded to an alkyl wherein said alkyl is bonded to the molecule of interest.
- [570] The term "sulfo" includes a sulfo group, $\text{-SO}_3\text{H}$, and its salts.
- [571] The term "sulfoalkyl" includes an alkyl group to which a sulfonate group is bonded, wherein said alkyl is bonded to the molecule of interest.
- [572] The term "aralkyl" includes aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Even more preferred are lower aralkyl radicals having phenyl

attached to alkyl portions having one to three carbon atoms. Examples of such radicals include benzyl, diphenylmethyl and phenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy. The term "arylalkenyl" includes aryl-substituted alkenyl radicals. Preferable arylalkenyl radicals are "lower arylalkenyl" radicals having aryl radicals attached to alkenyl radicals having

[573] The term "heterocyclalkyl" includes an alkyl radical that is substituted with one or more heterocycl groups. Preferable heterocyclalkyl radicals are "lower heterocyclalkyl" radicals having one or more heterocycl groups attached to an alkyl radical having one to ten carbon atoms.

[574] The term "heteroarylalkyl" includes an alkyl radical that is substituted with one or more heteroaryl groups. Preferable heteroarylalkyl radicals are "lower heteroarylalkyl" radicals having one or more heteroaryl groups attached to an alkyl radical having one to ten carbon atoms.

[575] The term "quaternary heterocyclalkyl" includes an alkyl radical that is substituted with one or more quaternary heterocycl groups. Preferable quaternary heterocyclalkyl radicals are "lower quaternary heterocyclalkyl" radicals having one or more quaternary heterocycl groups attached to an alkyl radical having one to ten carbon atoms.

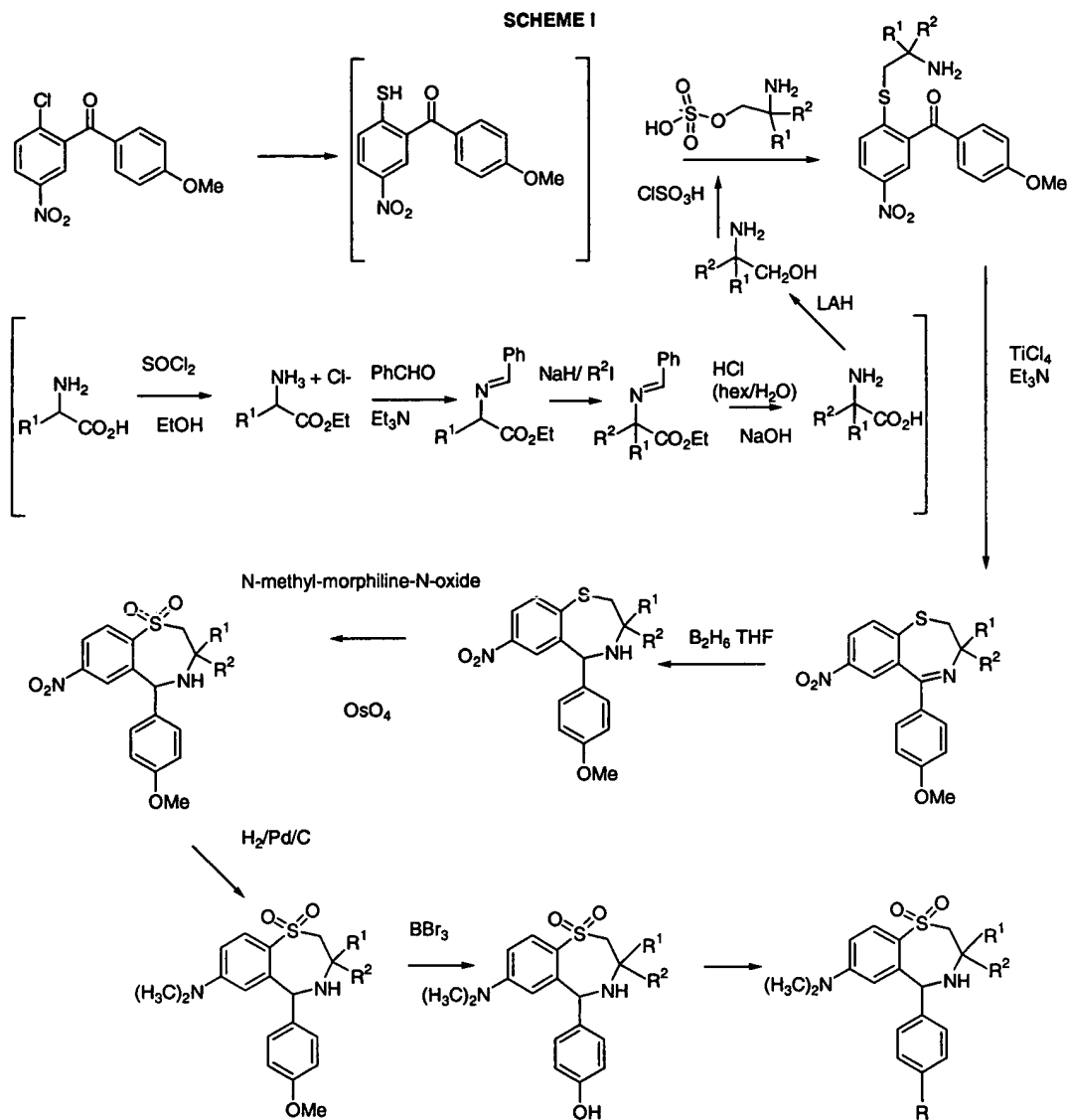
[576] The term "quaternary heteroarylalkyl" includes an alkyl radical that is substituted with one or more quaternary heteroaryl groups. Preferable quaternary heteroarylalkyl radicals are "lower quaternary heteroarylalkyl" radicals having one or more quaternary heteroaryl groups attached to an alkyl radical having one to ten carbon atoms.

[577] The term "alkylheteroarylalkyl" includes a heteroarylalkyl radical that is substituted with one or more alkyl groups. Preferable alkylheteroarylalkyl radicals are "lower alkylheteroarylalkyl" radicals with alkyl portions having one to ten carbon atoms.

[578] The term "alkoxy" includes an alkyl radical which is attached to the molecule of interest by oxygen, such as a methoxy radical. More preferred alkoxy radicals are

"lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, iso-propoxy, butoxy and *tert*-butoxy.

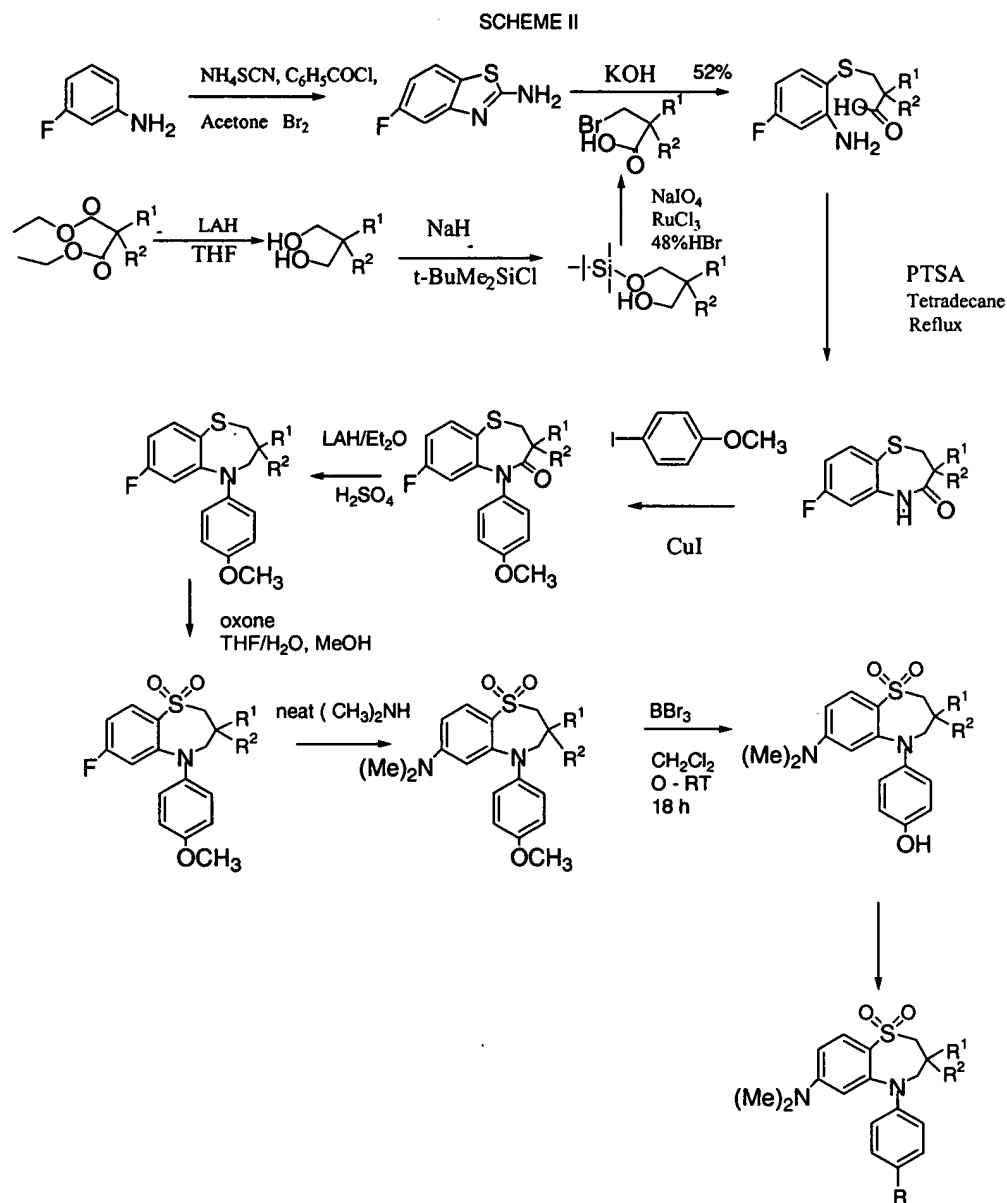
- [579] The term "carboxy" includes the carboxy group, $\text{-CO}_2\text{H}$, and its salts.
- [580] The term "carboxyalkyl" includes an alkyl radical that is substituted with one or more carboxy groups. Preferable carboxyalkyl radicals are "lower carboxyalkyl" radicals having one or more carboxy groups attached to an alkyl radical having one to six carbon atoms.
- [581] The term "carboxyheterocyclyl" includes a heterocyclyl radical that is substituted with one or more carboxy groups.
- [582] The term "carboxyheteroaryl" includes a heteroaryl radical that is substituted with one or more carboxy groups.
- [583] The term "carboalkoxyalkyl" includes an alkyl radical that is substituted with one or more alkoxycarbonyl groups. Preferable carboalkoxyalkyl radicals are "lower carboalkoxyalkyl" radicals having one or more alkoxycarbonyl groups attached to an alkyl radical having one to six carbon atoms.
- [584] The term "carboxyalkylamino" includes an amino radical that is mono- or di-substituted. When used in combination, for example "alkylaryl" or "arylalkyl," the individual terms listed above have the meaning indicated above.
- [585] The term "acyl" includes an organic acid group in which the hydroxy of the carboxy group has been removed. Examples of acyl groups include, but are not limited to, acetyl and benzoyl.
- [586] The term "hydrocarbyl" refers to radicals consisting exclusively of the elements carbon and hydrogen. These radicals include, for example, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, and aryl moieties. These radicals also include alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, and aryl moieties substituted with other aliphatic or cyclic hydrocarbon groups, such as alkaryl, alkenaryl and alkynaryl. Preferably, these moieties comprise 1 to 20 carbon atoms, 1-10 carbons or 1-6 carbons.



[593] The 5-position phenyl group of the 1,4-benzothiazepine intermediates of Scheme I can be further substituted (with R) as specifically disclosed in this application or, for example, by substituting the 5-position phenyl group through suitable modification of the methods disclosed in U.S. Patent 5,994,391 and WO99/64409.

[594] The synthetic methods for the preparation of 1,5-benzothiazepines disclosed, for example, in WO96/16051 and WO99/35135 can be modified as illustrated below and in the working examples to prepare the 1,5-benzothiazepine compounds of the present invention.

[595] In particular, the 1,5-benzothiazepine compounds of the present invention can be prepared as set forth in Scheme II below.



[596] The 5-position phenyl group of the 1,5-benzothiazepine intermediates can be can be further substituted (with R) as specifically disclosed in this application or, for

example, by substituting the 5-position phenyl group through suitable modification of the methods disclosed in U.S. Patent 5,994,391 and WO99/64409.

[597] Working Examples

[598] The following examples contain detailed descriptions of the methods of preparation of the compounds of the present invention. These detailed descriptions fall within the scope, and serve to exemplify, the above-described general synthetic procedures which form part of the invention. These detailed descriptions are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are in degrees centigrade unless otherwise indicated. The preparation of the reagents used in these Examples is either specifically disclosed herein or such reagents are commercially available.

[599] The following abbreviations are used in the examples below:

[600] Me - methyl

[601] Et - ethyl

[602] EtOH - ethanol

[603] Et₃N - triethylamine

[604] HCl - hydrochloric acid

[605] LAH - lithium aluminum hydride

[606] LiOH - lithium hydroxide

[607] MeOH - methanol

[608] NaOH - sodium hydroxide

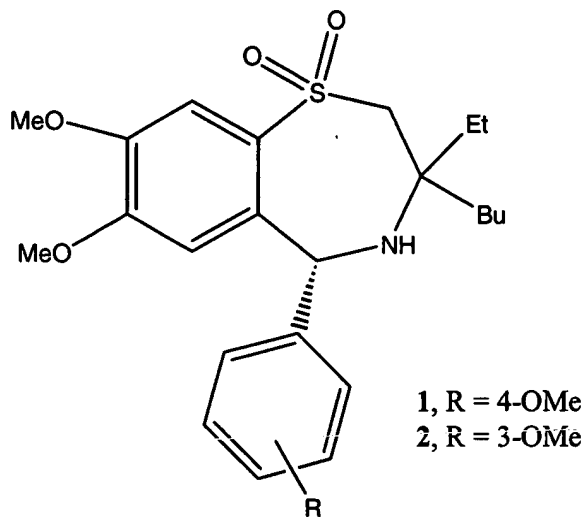
[609] Ph - phenyl

[610] PTSA - para-toluene sulfonic acid

[611] RT - room temperature

[612] THF - tetrahydrofuran

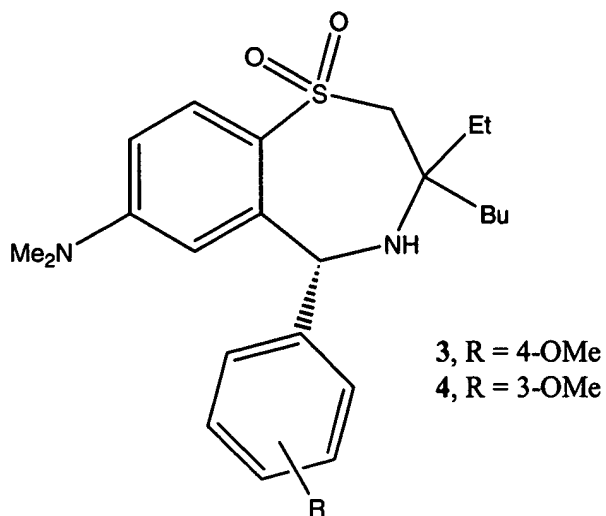
[613] Example 1



[614]

[615] Compounds 1 and 2 are prepared in accordance with the procedure set forth in Synthetic Example 1 of patent application WO96/05188, except that 4-methoxybenzoyl chloride and 3-methoxybenzoyl chloride, respectively, are substituted for benzoyl chloride in step (h).

[616] Example 2



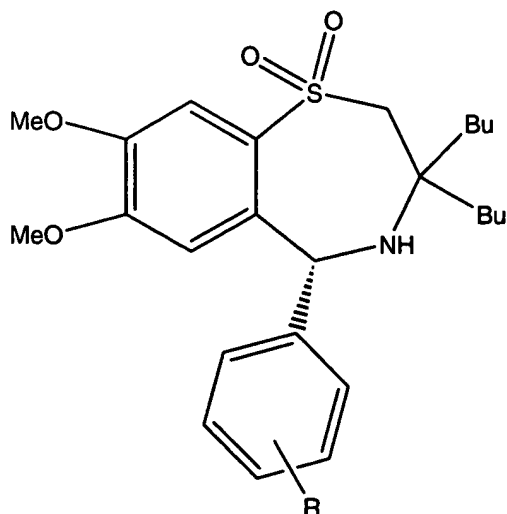
[617] Step 1: Preparation of 4-fluorophenyl substituted intermediate

[618] A 4-fluorophenyl substituted intermediate is prepared in accordance with the procedure set forth in Synthetic Example 1 of patent application WO96/05188, except that 4-fluorophenol is substituted for 3,4-dimethoxyphenol and 4-methoxybenzoyl chloride (or 3-methoxybenzoyl chloride) is substituted for benzoyl chloride in step (h) of Synthetic Example 1.

[619] Step 2: Preparation of dimethylamino-compound

[620] A Fisher porter bottle is fitted with a nitrogen line and magnetic stirrer. The system is purged with nitrogen. The 4-fluorophenyl substituted intermediate (62.6 mmol) obtained from Step 1 is added and the vessel is sealed and cooled to -78°C. Dimethylamine (17.1 g, 379 mmol) is condensed using a CO₂/acetone bath and added to the reaction vessel. The mixture is allowed to warm to room temperature and heated to 60°C. After 20 hours, the reaction mixture is allowed to cool and dissolved in ethyl ether. The ether solution is washed with water and then with saturated aqueous sodium chloride. It is then dried with magnesium sulfate, filtered, and concentrated *in vacuo* to give compound 3 (or compound 4 when 3-methoxybenzoyl chloride is used in Step 1).

[621] Example 3



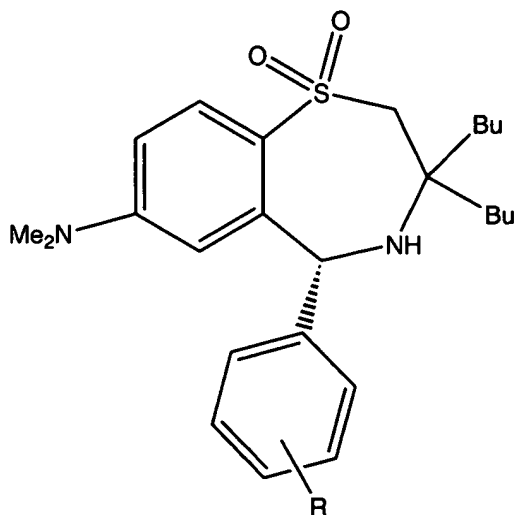
[622] Step 1: Preparation of 2-amino-2-butylhexyl hydrogen sulfate

[623] A 2-amino-2-butylhexyl hydrogen sulfate is prepared in accordance with the procedure set forth in steps (a) through (g) of Synthetic Example 1 of patent application WO96/05188, except that 2-aminohexanoic acid is substituted for 2-aminobutyric acid in step (a) of Synthetic Example 1.

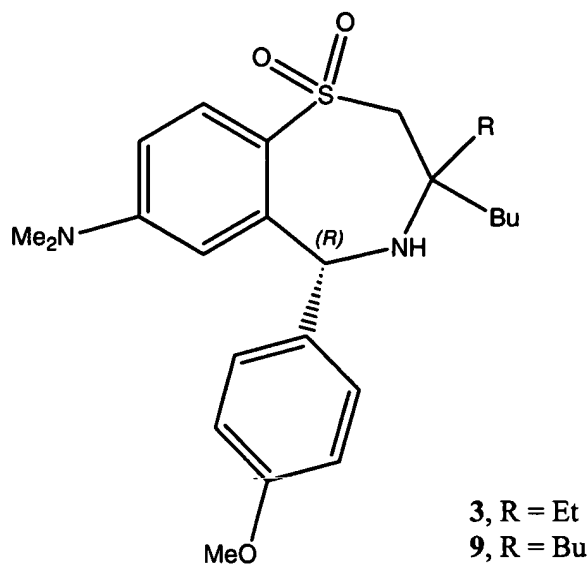
[624] Step 2: Preparation of the dimethoxybenzothiazepine

[625] Compounds 7 and 8 are prepared in accordance with the procedure set forth in steps (h) through (o) of Synthetic Example 1 of patent application WO96/05188, except that 2-amino-2-butylhexyl hydrogen sulfate (obtained from Step 1) is substituted for 2-amino-2-ethylhexyl hydrogen sulfate, and either 4-methoxybenzoyl chloride (for Compound 7) or 3-methoxybenzoyl chloride (for Compound 8) is substituted for benzoyl chloride in Step (h) of Synthetic Example 1.

[626] Example 4



9, R = 4-OMe
10, R = 3-OMe,



[632] Step 1: Preparation of chlorobenzophenone

[633] In an inert atmosphere, 68.3 g of phosphorus pentachloride (0.328mole Aldrich 15,777-5) is placed into a 2-necked 500 mL round bottom flask. The flask is fitted with a nitrogen inlet adapter and suba seal. The flask is removed from the inert atmosphere and a nitrogen purge is begun. 50 mL of anhydrous chlorobenzene (Aldrich 28,451-3) is added to the phosphorus pentachloride via syringe and the solution is stirred with a magnetic stir bar. 60 g of 2-chloro-5-nitrobenzoic acid (0.298 mole Aldrich 12,511-3) is slowly added to the chlorobenzene solution under nitrogen purge. After stirring at room temperature for about 20 hours, the solution is placed in an oil bath and heated at 50°C for 1 hour. The chlorobenzene is removed from the solution by high vacuum. The residue is washed with anhydrous hexane to yield a dry acid chloride having a weight of 61.95 g. The acid chloride is stored in an inert and dry atmosphere.

[634] In an inert atmosphere, the acid chloride is mixed with 105 mL of anhydrous anisole (0.97 mole Aldrich 29,629-5) in a 2-necked 500 mL round bottom flask. The flask is

fitted with an addition funnel and a nitrogen inlet adapter and removed from inert atmosphere. The reaction solution is chilled with an ice bath and a nitrogen purge is begun. 45.1 g of aluminum chloride (0.34 moles Aldrich 29,471-3) is placed in a solid addition funnel and the aluminum chloride is slowly added to the chilled solution. After the addition is complete, the solution is allowed to warm to room temperature and stirred overnight. The reaction is quenched by pouring the solution into a mixture of 300 mL 1N HCl and ice. The resulting solution is stirred for 15 minutes and extracted twice with ether. The organic layers are combined and extracted twice with 2% sodium hydroxide, and then twice with deionized water. The extracted organic layer is then dried with magnesium sulfate, filtered and further dried using a rotovap. Remaining anisole is then removed by high vacuum. The resulting product is crystallized from 90% ethanol 10% ethyl acetate and dried on a vacuum line.

[635] Step 2: Preparation of thiobenzophenone intermediate

[636] 10.12 g (0.036 moles) of the chlorobenzophenone intermediate obtained from Step 1 is combined with 200 mL of anhydrous dimethylsulfoxide and placed in a 500 mL round bottom flask equipped with a magnetic stir bar. The flask is fitted with a water condenser, nitrogen inlet, and stopper. 1.84 g of Li_2S (0.040 moles Aldrich 21,324-1) is added. The flask is placed in an oil bath and heated overnight at 75 °C under nitrogen. The solution is cooled to room temperature. 500 mL of 5% acetic acid is prepared in a 2 liter beaker and then added slowly to the solution in the flask while stirring is maintained in the flask. After 30 minutes, the solution is extracted with ether three times, dried (magnesium sulfate), filtered and concentrated *in vacuo* to give a thiobenzophenone intermediate.

[637] Step 3: Preparation of thioamine intermediate

[638] A solution of the thiobenzophenone intermediate (198 mmol, obtained from Step 2) in butyl acetate (300 mL) is added to a solution of the ethyl-butyl amine (for compound 3) or butyl-butyl amine (for compound 9) (obtained as set forth in Synthetic Example 1 of WO96/05188 or in Example 3, Step 1 of the present application) in water (250 mL). The reaction mixture is stirred and heated to 93°C. Sodium hydroxide (18.9 g)

in water (250 mL) is added dropwise. After complete addition, the reaction is stirred an additional 25 minutes at 93°C and then cooled to room temperature. The organic layer is separated, dried and concentrated to give a thioamine intermediate.

[639] Step 4: Preparation of the cyclic imine intermediate

[640] The thioamine intermediate (194 mmol, obtained from Step 3) is dissolved in 2,6-lutidine. p-Toluenesulfonic acid (0.70 g) is added and the reaction mixture is refluxed using a Dean Stark trap. After 22 hours of refluxing, the reaction mixture is concentrated *in vacuo*. Chromatography on silica gel gives the purified cyclic imine intermediate.

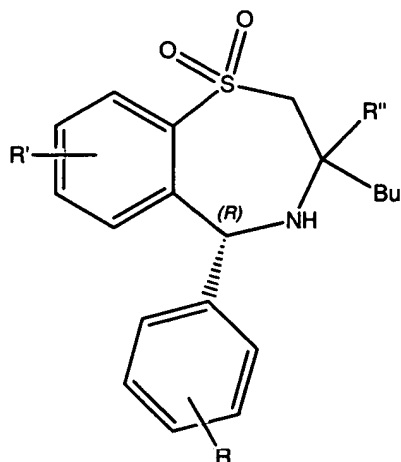
[641] Step 5: Preparation of the cyclic amine intermediate

[642] A 1M solution of diborane in tetrahydrofuran (200 mL) is added to a solution of the cyclic imine intermediate (167 mmol, obtained from Step 4) in tetrahydrofuran (350 mL). The reaction mixture is stirred at room temperature for 17 hours and then 6N HCl (150 mL) is added. The tetrahydrofuran is removed under reduced pressure and the aqueous residue basified with 50% sodium hydroxide. The resulting solution is extracted with ethyl acetate and the ethyl acetate layer is separated, dried and concentrated *in vacuo*. Purification by chromatography on silica gel gives the cyclic amine intermediate.

[643] Step 6: Preparation of the sulfone intermediate

[644] A solution of the cyclic amine intermediate (66.2 mmol, obtained from Step 5) in trifluoroacetic acid (125 mL) is added to 30% water (18.8 g) in trifluoroacetic acid (100 mL). The reaction mixture is stirred at room temperature for 17 hours and then poured into water (800 mL). 50% sodium hydroxide is then added until the mixture reaches a pH of 10. The reaction mixture is layered with ethyl acetate and stirred for 1 hour. The organic layer is separated, dried and concentrated *in vacuo*. The residue is purified by recrystallization or chromatography on silica gel to give the desired sulfone intermediate.

[645] Step 7: Preparation of the dimethylamino-benzothiazepine



- 13, R = 4-OH, R' = 3,4-dihydroxy, R'' = Et
 14, R = 3-OH, R' = 3,4-dihydroxy, R'' = Et
 15, R = 4-OH, R' = 4-(dimethylamino), R'' = Et
 16, R = 3-OH, R' = 4-(dimethylamino), R'' = Et
 17, R = 4-OH, R' = 3,4-dihydroxy, R'' = Bu
 18, R = 3-OH, R' = 3,4-dihydroxy, R'' = Bu
 19, R = 4-OH, R' = 4-(dimethylamino), R'' = Bu
 20, R = 3-OH, R' = 4-(dimethylamino), R'' = Bu

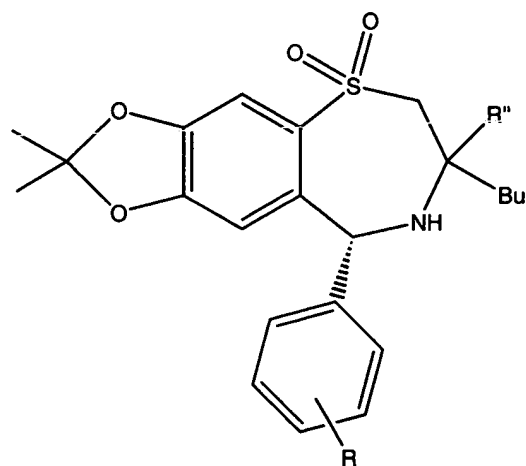
[646] The sulfone intermediate (20.4 mmol, obtained from Step 6) and ethanol (160 mL) are placed in a 300 mL Parr reactor. Formaldehyde (15.3 mL, 189 mmol, 37 weight percent in water) and 10% Pd/Carbon (1.45 g) are added. The reactor is heated to 55°C under hydrogen overnight. The reactor is cooled and purged with nitrogen. The solution is filtered through celite while washing with ether. The mixture is concentrated *in vacuo*, redissolved with ether, and washed with water. The organic layer is dried (magnesium sulfate), filtered and concentrated *in vacuo* to give the desired dimethylamino-benzothiazepine 3 or 9.

[647] Example 6

[648] A 250-mL, 3-neck, round-bottom flask is equipped with a nitrogen gas adaptor and magnetic stirrer. The system is purged with nitrogen. The corresponding methoxy-compound 1, 2, 3, 4, 7, 8, 9 or 10 (14.0 mmol) and trichloromethane (150 mL) are added to the flask. The reaction mixture is cooled to -78°C and boron tribromide (10.50 g/41.9 mmol per methoxy group) is added. The mixture is allowed to warm to

room temperature. After 4 hours, the reaction mixture is cooled to 0°C and quenched with 10% K₂CO₃ (100 mL). After 10 minutes, the layers are separated and the aqueous layer is extracted two times with ethyl ether. The trichloromethane and ether extracts are combined, washed with saturated aqueous sodium chloride, dried (magnesium sulfate), filtered, and concentrated *in vacuo* to give the desired product 13, 14, 15, 16, 17, 18, 19 or 20. See, M. Kitamura et al., *J. Am. Chem. Soc.*, **106**, 3252-57 (1984).

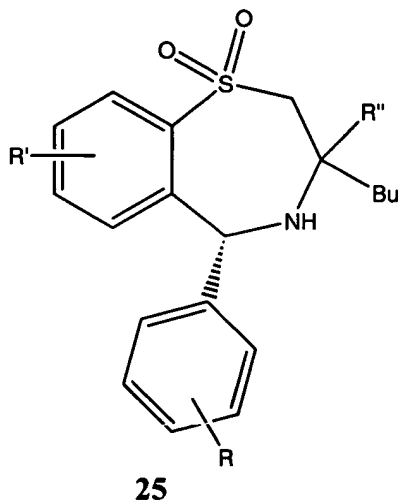
[649] Example 7



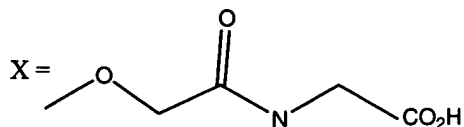
- 21, R = 4-OH, R'' = Et
 22, R = 3-OH, R'' = Et
 23, R = 4-OH, R'' = Bu
 24, R = 3-OH, R'' = Bu

[650] A 250-mL, 3-neck, round-bottom flask is equipped with a nitrogen gas adaptor and magnetic stirrer. The system is purged with nitrogen. The corresponding hydroxy-compound 13, 14, 17 or 18 (14.0 mmol) and dimethylformamide (150 mL) are added to the flask. The reaction mixture is cooled to 5°C. Acetone (48 mL), 2,2-dimethoxypropane (9.6 mL), and pyridinium p-toluenesulfonate (0.54 g) are added to the reaction mixture. After 24 hours, Amberlite IRA 402 (a strongly basic anion exchanger, quaternary ammonium type resin, chloride form, available from Sigma Chemical) is added to neutralize the catalyst. After 24 hours, the resin is removed by filtration, and the filtrate concentrated *in vacuo* to give the desired product 21, 22, 23 or 24. See, M. Kitamura et al., *J. Am. Chem. Soc.*, **106**, 3252-57 (1984).

[651] Example 8



R = 4-X or 3-X
R' = 3,4-dihydroxy or 4-(dimethylamino)
R'' = Et or Bu



[652] Step 1: Preparation of glycine ester intermediate

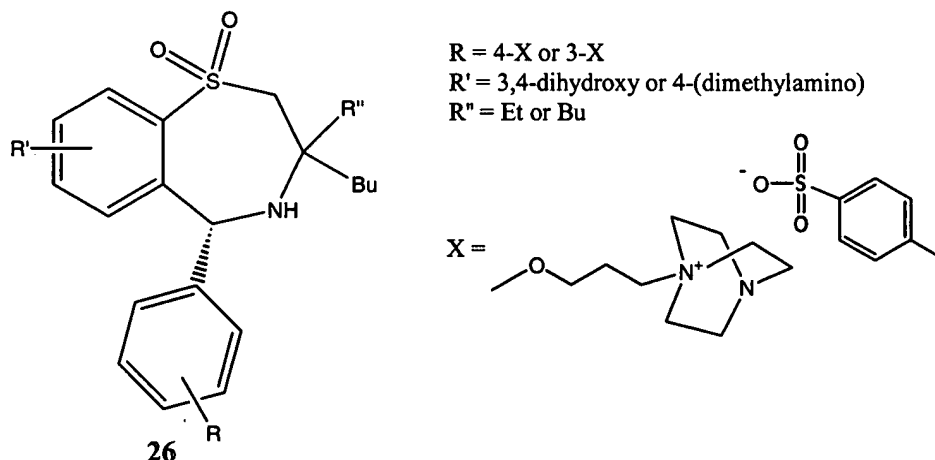
[653] To a solution of (13.9 mmol) of 15, 16, 19, 20, 21, 22, 23 or 24 (obtained from Example 6 or 7) and 2.9 g (21.0 mmol) of potassium carbonate in 100 mL of acetone is added 3.8 g (21.0 mmol) of N-(chloroacetyl)glycine ethyl ester and 50 mg (0.14 mmol) of tetrabutylammonium iodide. The reaction mixture is heated to reflux for 2 days, cooled to ambient temperature and stirred for 20 hours. It is then partitioned between ethyl acetate and water. The organic layer is washed with brine, dried over magnesium sulfate, and concentrated *in vacuo* to afford a glycine ester intermediate.

[654] Step 2: Preparation of acid

[655] A solution of the glycine ester intermediate (12.1 mmol, obtained from Step 1) and 1.5 g LiOH·H₂O (36.3 mmol) in 60 mL of tetrahydrofuran and 60 mL of water is heated to 45°C for 2 hours. The solution is then cooled to ambient temperature, acidified with 1 N HCl and partitioned between ethyl acetate and water. The organic

layer is washed with brine, dried over magnesium sulfate, and concentrated *in vacuo* to give the desired compound **25**. For reactions with reagents **21**, **22**, **23** or **24**, removal of the acetonide protecting group is accomplished by dissolving the substrate in 4:1 tetrahydrofuran/water at 0°C, adding excess trifluoroacetic acid, and stirring at room temperature overnight. The reaction is neutralized with ammonium hydroxide, and the tetrahydrofuran removed under reduced pressure. The product is then extracted into ethyl acetate, and concentrated *in vacuo* to give the desired product **25**. See, e.g., Y. Leblanc et al., *J. Org. Chem.*, **51**, 189-93 (1986).

[656] Example 9



[657] Step 1: Preparation of propyl tosylate intermediate

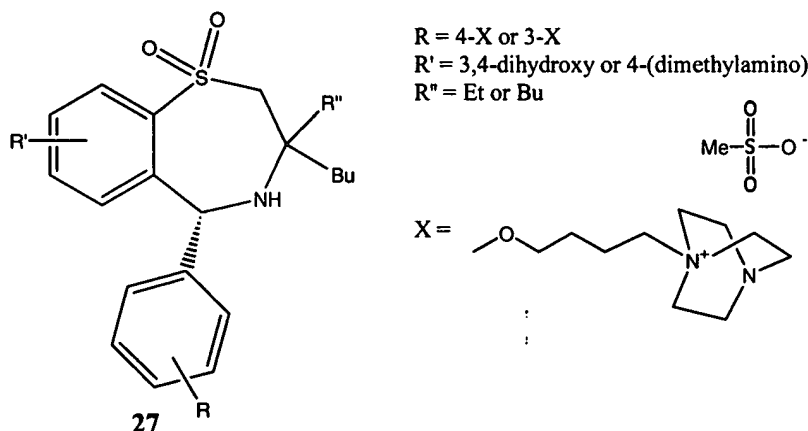
[658] A solution of **15**, **16**, **19**, **20**, **21**, **22**, **23** or **24** (10.9 mmol, obtained from Example 6 or 7) in acetone (100 mL) at 25°C under nitrogen is treated with powdered K₂CO₃ (3.8 g, 27.2 mmol, 2.5 equivalents) and 1,3-propanediol di-*p*-tosylate (13.0 g, 32.6 mmol, 3.0 equivalents), and the resulting mixture is stirred at 65°C for 21 hours. The cream-colored slurry is cooled to 25°C and is filtered through a sintered glass funnel. The filtrate is concentrated and the residue dissolved in ethyl acetate (150 mL). The organic layer is washed with saturated aqueous sodium bicarbonate (2 x 150 mL) and saturated aqueous sodium chloride (2 x 150 mL), and is dried (magnesium sulfate) and concentrated *in vacuo* to afford a propyl tosylate intermediate. For reactions with reagents **21**, **22**, **23** or **24**, removal of the acetonide protecting group is accomplished

by dissolving the substrate in 4:1 tetrahydrofuran/water at 0°C, adding excess trifluoroacetic acid, and stirring at room temperature overnight. The reaction is neutralized with ammonium hydroxide, and the tetrahydrofuran removed under reduced pressure. The product is then extracted into ethyl acetate, and concentrated *in vacuo* to give a propyl tosylate intermediate. See, e.g., Y. Leblanc et al., *J. Org. Chem.*, **51**, 189-93 (1986).

[659] Step 2: Preparation of quaternary salt

[660] A solution of the propyl tosylate intermediate (1.56 mmol, obtained from Step 1) in acetonitrile (15 mL) at 25°C under nitrogen is treated with diazabicyclo[2.2.2]octane ("DABCO", 0.26 g, 2.34 mmol, 1.5 equivalents) and stirred at 50°C for 6 hours and then at 25°C for 14 hours. The pale amber solution is cooled to 25°C and concentrated *in vacuo* to give the desired compound 26.

[661] Example 10



[662] Step 1: Preparation of butyl mesylate intermediate

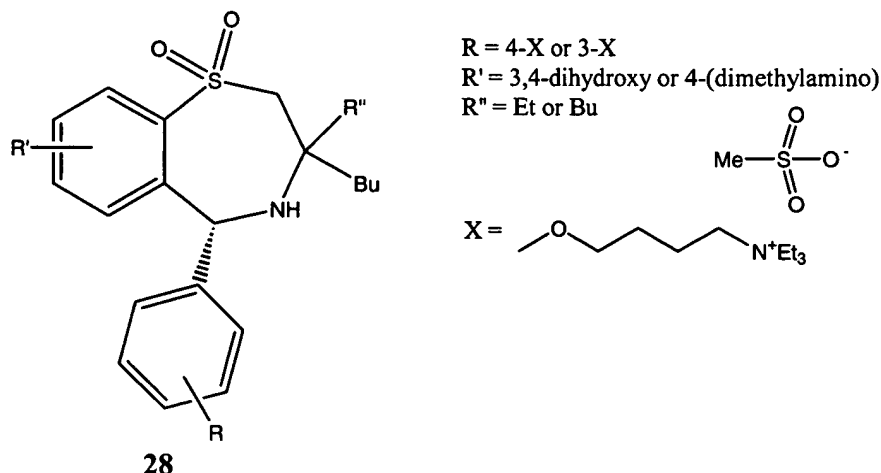
[663] A mixture of 2.18 mmol of 15, 16, 19, 20, 21, 22, 23 or 24 (obtained from Example 6 or 7), 2.68 g (10.88 mmol) of busulfan, and 1.50 g (10.88 mmol) of potassium carbonate in 20 mL of acetone is stirred at reflux overnight. The mixture is concentrated *in vacuo* and the crude is dissolved in 30 mL of ethyl acetate. The insoluble solid is filtered off and the filtrate is concentrated *in vacuo*. The resulting white foam is chromatographed through a silica gel column and eluted with 30% ethyl

acetate/hexane to give the butyl mesylate intermediate. For reactions with reagents **21**, **22**, **23** or **24**, removal of the acetonide protecting group is accomplished by dissolving the substrate in 4:1 tetrahydrofuran/water at 0°C, adding excess trifluoroacetic acid, and stirring at room temperature overnight. The reaction is neutralized with ammonium hydroxide, and the tetrahydrofuran removed under reduced pressure. The product is then extracted into ethyl acetate and concentrated *in vacuo* to give a butyl mesylate intermediate. See, e.g., Y. Leblanc et al., *J. Org. Chem.*, **51**, 189-93 (1986).

[664] Step 2: Preparation of quaternary salt

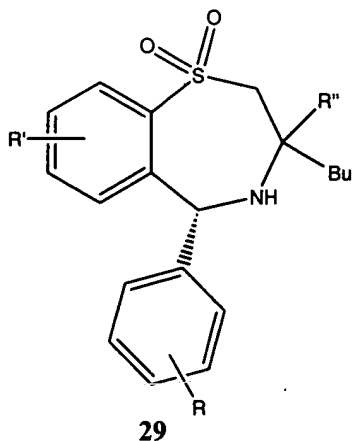
[665] A solution of 0.85 mmol of the butyl mesylate intermediate (obtained from Step 1) and 191 mg (1.71 mmol) of diazabicyclo[2.2.2]octane in 10 mL of acetonitrile is stirred at 80°C for 4 hours. The reaction mixture is concentrated *in vacuo* to yield a white foam. The foam is crushed and washed with ether. The solid is filtered off and dried *in vacuo* to give the desired compound **27**.

[666] Example 11

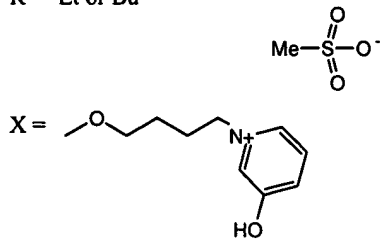


[667] A solution of 1.64 mmol of the butyl mesylate intermediate (obtained from Example 10, Step 1) and 15 mL of triethylamine in 10 mL of acetonitrile is heated at 50°C for 2 days. The solvent is evaporated and the residue triturated with ether and ethyl acetate to afford the desired product **28**.

[668] Example 12

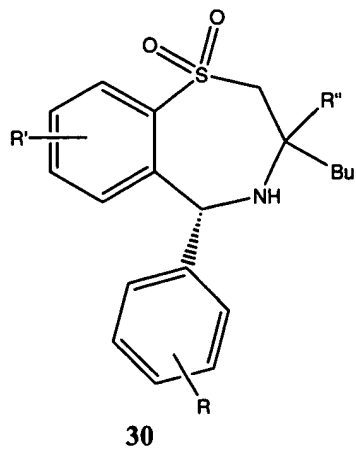


R = 4-X or 3-X
 R' = 3,4-dihydroxy or 4-(dimethylamino)
 R'' = Et or Bu

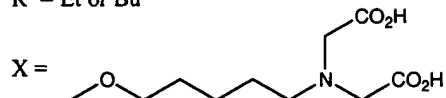


[669] A solution of 1.64 mmol of the butyl mesylate intermediate (obtained from Example 10, Step 1) and 234 mg (2.46 mmol) of 3-hydroxy-pyridine in 1 mL of dimethylformamide is heated at 70°C for 20 hours. The solvent is evaporated and the residue triturated with ether and ethyl acetate to afford the desired product **29**.

[670] Example 13



R = 4-X or 3-X
 R' = 3,4-dihydroxy or 4-(dimethylamino)
 R'' = Et or Bu



[671] Step 1: Preparation of pentyl bromide intermediate

[672] 13.1 mmol of **15**, **16**, **19**, **20**, **21**, **22**, **23** or **24** (obtained from Example 6 or 7) is added to a stirred solution of 0.63 g (15.72 mmol, 60% dispersion) of sodium hydride in 85 mL of dimethylformamide. The resulting solution is stirred at ambient temperature for 1 hour. 37.7 g (163.75 mmol) of 1,5-dibromopentane is added to the solution and the solution stirred overnight at ambient temperature. The dimethylformamide is removed *in vacuo* and the residue is extracted with ethyl acetate and washed with brine. The extract is dried over magnesium sulfate, and the concentrated residue purified by column chromatography to give a pentyl bromide intermediate.

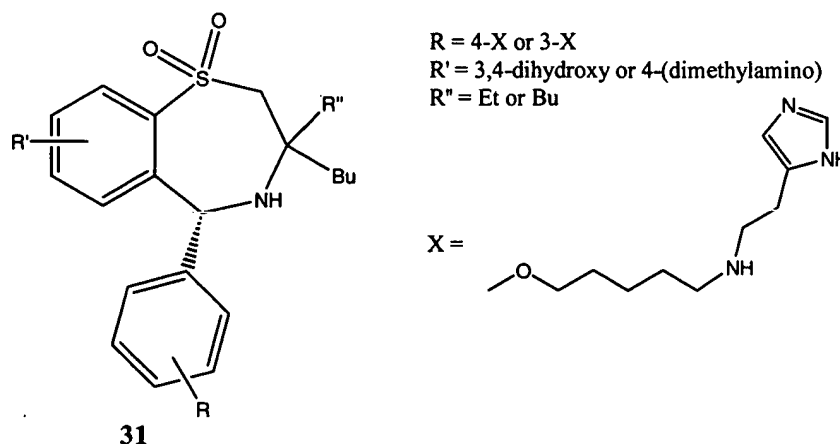
[673] Step 2: Preparation of diester intermediate

[674] A mixture of 14.1 mmol of the pentyl bromide intermediate (obtained from Step 1), 65 g (0.35 mol) of diethylaminodiacetate and 7.5 g (71 mmol) of anhydrous Na₂CO₃ is stirred at 160°C for 3 hours. The reaction mixture is diluted with water and extracted with methylene chloride. The volatiles are removed *in vacuo* to give the diester intermediate. For reactions with reagents **21**, **22**, **23** or **24**, removal of the acetonide protecting group is accomplished by dissolving the substrate in 4:1 tetrahydrofuran/water at 0°C, adding excess trifluoroacetic acid, and stirring at room temperature overnight. The reaction is neutralized with ammonium hydroxide, and the tetrahydrofuran removed under reduced pressure. The product is then extracted into ethyl acetate and concentrated *in vacuo* to give a diester intermediate. See, e.g., Y. Leblanc et al., *J. Org. Chem.*, **51**, 189-93 (1986).

[675] Step 3: Preparation of diacid

[676] The mixture of the diester intermediate (obtained from Step 2) and 2.7 g (64.3 mmol) of lithium hydroxide in tetrahydrofuran (75 mL) and water (50 mL) is stirred at 40°C for 18 hours. The reaction mixture is acidified with 1% HCl and extracted with methylene chloride. The residue is triturated with hexane and filtered to give the desired compound **30**.

[677] Example 14



[678] Step 1: Preparation of pentyl iodide intermediate

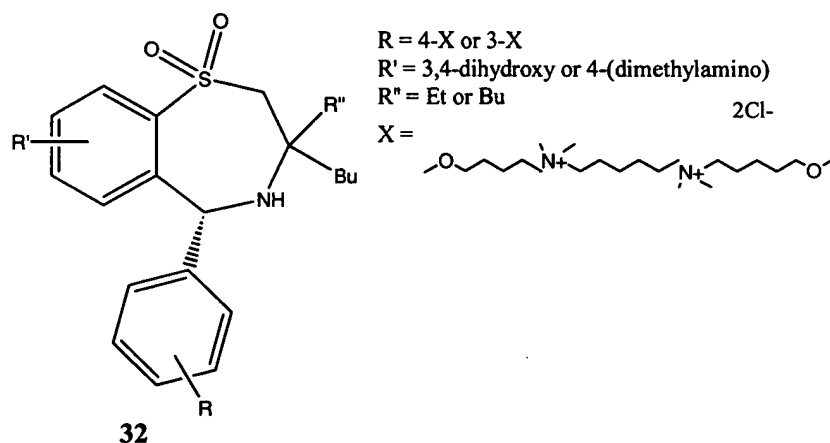
[679] To a solution of **15**, **16**, **19**, **20**, **21**, **22**, **23** or **24** (6.53 mmol, obtained from Example 6 or 7) in 100 mL of dimethylformamide is added 198 mg (7.83 mmol) of 95% sodium hydride. The mixture is stirred 15 minutes at room temperature and diiodopentane is added. After 1 hour at room temperature the mixture is diluted in ethyl acetate and water. The aqueous layer is extracted with ethyl acetate and the combined organic layer washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue is chromatographed over silica gel, eluting with hexane/ethyl acetate (1/5) to afford a pentyl iodide intermediate. For reactions with reagents **21**, **22**, **23** or **24**, removal of the acetonide protecting group is accomplished by dissolving the substrate in 4:1 tetrahydrofuran/water at 0°C, adding excess trifluoroacetic acid, and stirring at room temperature overnight. The reaction is neutralized with ammonium hydroxide, and the tetrahydrofuran removed under reduced pressure. The product is then

extracted into ethyl acetate, and concentrated *in vacuo* to give the pentyl iodide intermediate. See, e.g., Y. Leblanc et al., *J. Org. Chem.*, **51**, 189-93 (1986).

[680] Step 2: Preparation of amino-histamine

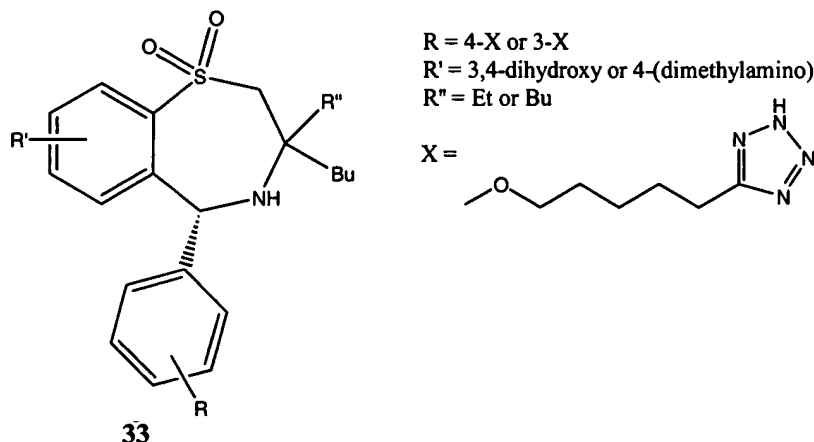
[681] A solution of the pentyl iodide intermediate (1.53 mmol, obtained from Step 1) and 3.4 g (30.6 mmol) of histamine is heated to 50°C for 17 hours. The mixture is dissolved in ethyl acetate and saturated sodium bicarbonate. The organic layer is washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue is triturated with ether to afford the desired compound 31.

[682] Example 15



[683] The pentyl bromide intermediate (1.64 mmol, obtained from Example 13, Step 1) and N,N,N',N'-tetramethyl-1,6-hexanediamine (0.100 g, 0.580 mmol) in 5 mL of acetonitrile are placed in a 4 oz. Fischer Porter bottle. The reaction vessel is purged with nitrogen, sealed, equipped with magnetic stirrer and heated to 50°C. After 15 hours, the reaction mixture is cooled to ambient temperature and concentrated *in vacuo* to give a foamy solid. The solid is dissolved in acetonitrile and precipitated with ethyl ether to give the desired dibromide salt. The dibromide salt is converted to its corresponding dichloride salt using Biorad AG 2-X8 resin (a quaternary ammonium styrene type resin, chloride form, available from Biorad Laboratories) and eluting with 70% H₂O/CH₃CN to give the desired compound 32.

[684] Example 16



[685] Step 1: Preparation of pentyl bromide intermediate

[686] To a stirred suspension of 1.01 g (25.4 mmol, 60% oil dispersion) of sodium hydride in 150 mL of dimethylformamide is added 19.5 mmol of 15, 16, 19, 20, 21, 22, 23 or 24 (obtained from Example 6 or 7) in portions. After 30 minutes, the reaction mixture is cooled in a water bath (15°C) and 4.48 g (195 mmol) of 1,5-dibromopentane is added. The reaction mixture is stirred at ambient temperature for 1.5 hours and quenched with 50 mL of saturated ammonium chloride. The reaction mixture is then diluted with ethyl acetate, washed with water, washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to a pentyl bromide intermediate.

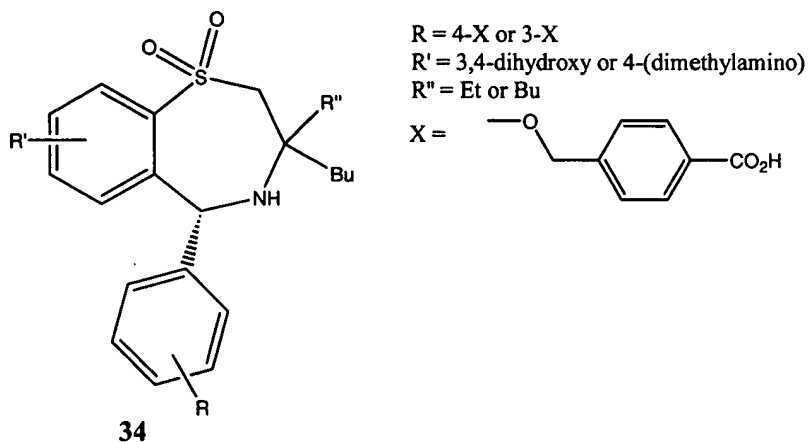
[687] Step 2: Preparation of pentyl nitrile intermediate

[688] To a stirred solution of 0.621 mmol of the pentyl bromide intermediate (obtained from Step 1) in 1 mL of dimethylsulfoxide is added 37 mg (0.745 mmol) of sodium cyanide. The reaction mixture is stirred at ambient temperature for 16 hours. The reaction mixture is concentrated under a nitrogen stream and the residue partitioned between ethyl acetate and water. The organic layer is washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford a pentyl nitrile intermediate.

[689] Step 3: Preparation of tetrazole

[690] A solution of 0.5 mmol of the pentyl nitrile intermediate (obtained from Step 2) and 666 mg (3.23 mmol) of azidotrimethyltin in 5 mL of toluene is stirred with heating at 80°C for 60 hours. The reaction mixture is concentrated under a nitrogen stream. Purification by reversed phase chromatography (Waters-Delta preparative scale HPLC) using 60% water/acetonitrile yields the desired compound 33. For reactions with reagents 21, 22, 23 or 24, removal of the acetonide protecting group is accomplished by dissolving the substrate in 4:1 tetrahydrofuran/water at 0°C, adding excess trifluoroacetic acid, and stirring at room temperature overnight. The reaction is neutralized with ammonium hydroxide, and the tetrahydrofuran removed under reduced pressure. The product is then extracted into ethyl acetate and concentrated *in vacuo* to give the desired compound 33. See, e.g., Y. Leblanc et al., *J. Org. Chem.*, **51**, 189-93 (1986).

[691] Example 17



[692] Step 1: Preparation of benzoate intermediate

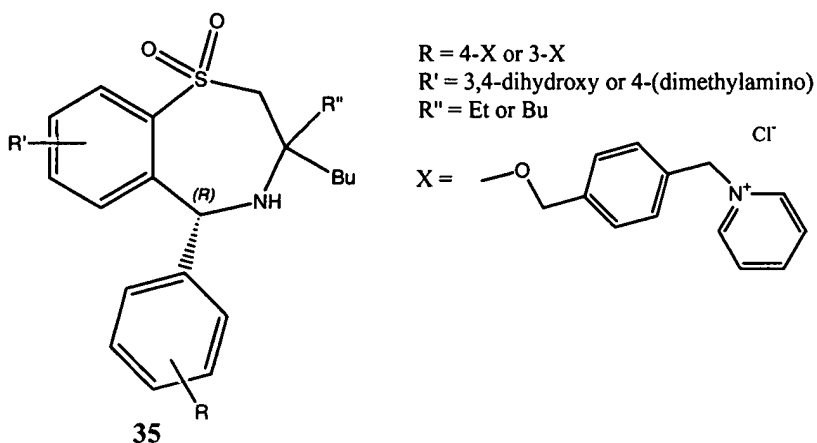
[693] To a solution of 1.15 mmol of 15, 16, 19, 20, 21, 22, 23 or 24 (obtained from Example 6 or 7) in 10 mL dimethylformamide is added 35 mg (1.39 mmol) of 95%

sodium hydride. The reaction mixture is stirred for 10 minutes. To the reaction mixture is added 525 mg (2.29 mmol) of methyl 4-(bromomethyl)benzoate and the reaction mixture is stirred for an additional 16 hours. Water (100 mL) is added to the reaction mixture. The reaction mixture is extracted with ethyl acetate, washed with brine, dried over magnesium sulfate, filtered and the solvent evaporated to afford a benzoate intermediate. For reactions with reagents **21**, **22**, **23** or **24**, removal of the acetonide protecting group is accomplished by dissolving the substrate in 4:1 tetrahydrofuran/water at 0°C, adding excess trifluoroacetic acid, and stirring at room temperature overnight. The reaction is neutralized with ammonium hydroxide, and the tetrahydrofuran removed under reduced pressure. The product is then extracted into ethyl acetate, and concentrated *in vacuo* to give a benzoate intermediate. See, e.g., Y. Leblanc et al., *J. Org. Chem.*, **51**, 189-93 (1986).

[694] Step 2: Preparation of acid

- [695]** A solution of 0.84 mmol of the benzoate intermediate (obtained from Step 1) and 325 mg (2.53 mmol) of KOSi(CH₃)₃ (Aldrich) in 16 mL tetrahydrofuran is stirred for 3.5 hours. The tetrahydrofuran is evaporated and water is added. The solution is extracted with ethyl acetate, dried over magnesium sulfate, filtered and the solvent evaporated to afford the desired compound **34**.

[696] Example 18



[697] Step 1: Preparation of chlorobenzyl intermediate

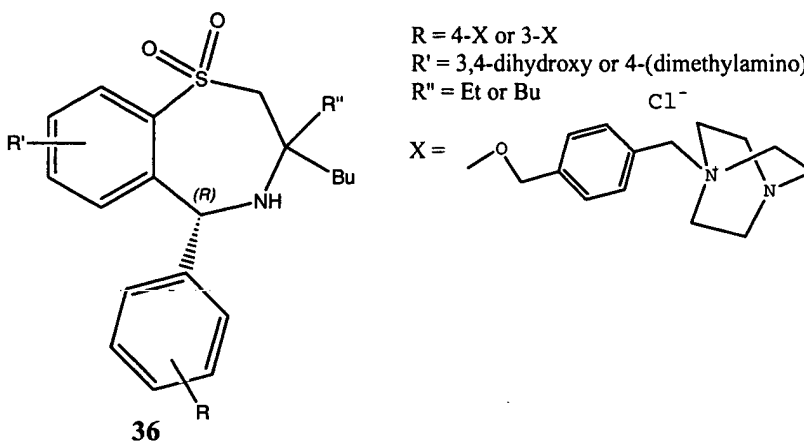
[698] A solution of **15**, **16**, **19**, **20**, **21**, **22**, **23** or **24** (10.9 mmol, obtained from Example 6 or 7) in acetone (100 mL) at 25°C under nitrogen is treated with powdered K_2CO_3 (2.3 g, 16.3 mmol, 1.5 equivalents) and *a,a'*-dichloro-*p*-xylene (6.7 g, 38.1 mmol, 3.5 equivalents) and the resulting solution is stirred at 65°C for 48 hours. The reaction mixture is cooled to 25°C and concentrated to 1/5 of its original volume. The residue is dissolved in ethyl acetate (150 mL) and washed with water (2 x 150 mL). The aqueous layer is extracted with ethyl acetate (2 x 150 mL) and the combined organic extracts are washed with saturated aqueous sodium chloride (2 x 150 mL). The combined extracts are dried (magnesium sulfate) and concentrated *in vacuo* to provide a chlorobenzyl intermediate. For reactions with reagents **21**, **22**, **23** or **24**, removal of the acetonide protecting group is accomplished by dissolving the substrate in 4:1 tetrahydrofuran/water at 0°C, adding excess trifluoroacetic acid, and stirring at room temperature overnight. The reaction is neutralized with ammonium hydroxide, and the tetrahydrofuran removed under reduced pressure. The product is then extracted into ethyl acetate and concentrated *in vacuo* to give a chlorobenzyl intermediate. See, e.g., Y. Leblanc et al., *J. Org. Chem.*, **51**, 189-93 (1986).

[699] Step 2: Preparation of quaternary salt

[700] A solution of the chlorobenzyl intermediate (1.7 mmol, obtained from Step 1) in acetonitrile (5 mL) at 25°C under nitrogen is treated with pyridine (5 mL) and stirred

at 35°C for 36 hours. The pale amber solution is cooled to 25°C and concentrated *in vacuo* to give the desired compound 35.

[701] Example 19

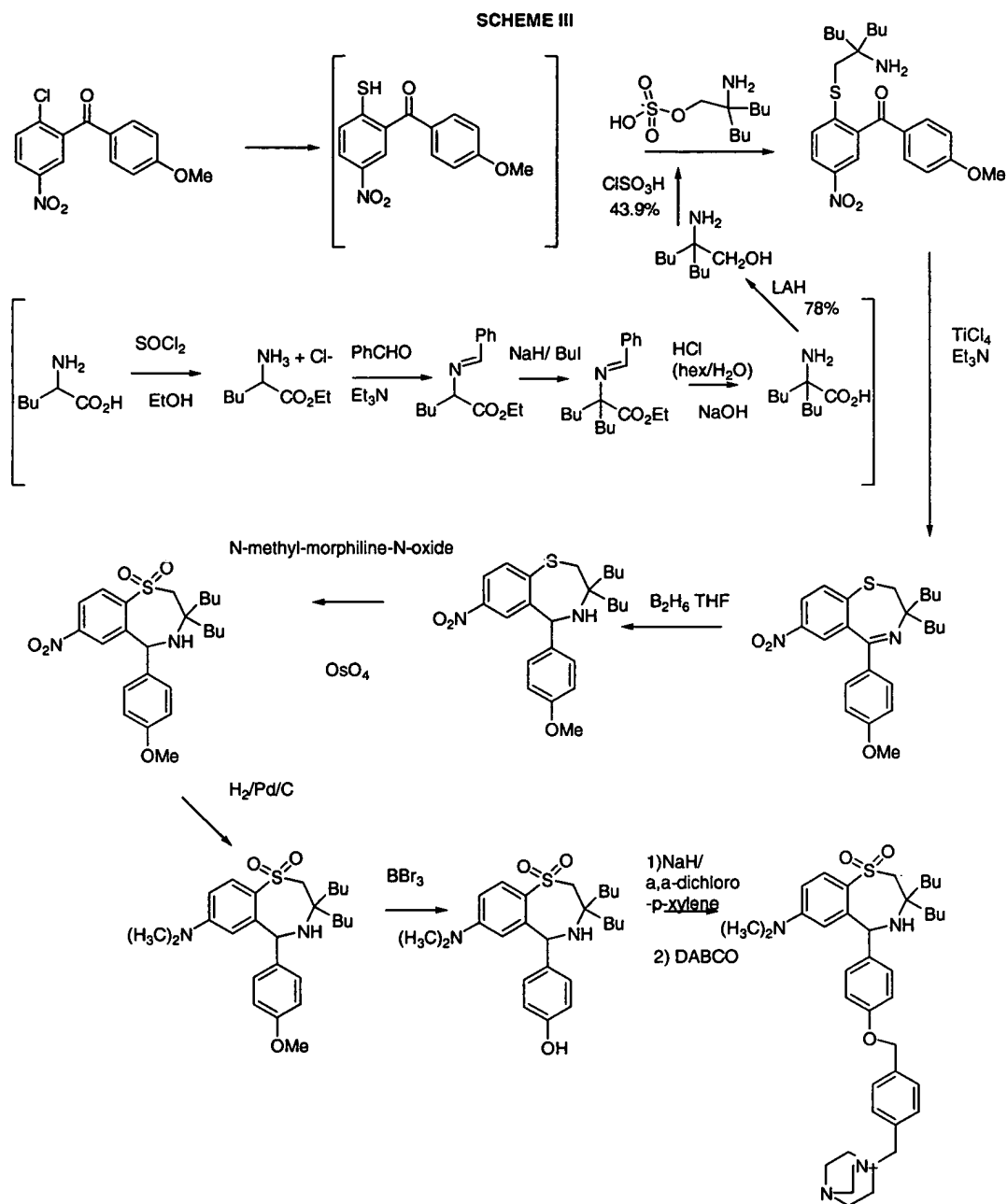


[702] Under nitrogen, a solution of 14.5 mmol of the chlorobenzyl intermediate (obtained from a procedure similar to the one outlined in Example 18, Step 1) in 60 mL of acetonitrile is added dropwise over a 30 minute period to a solution of 2.9 g (26.2 mmol) of diazabicyclo[2.2.2]octane in 40 mL of acetonitrile at 35°C. During the addition, a colorless precipitate is formed. The slurry is stirred at 35°C for an additional 2 hours. The product is collected and washed with 1 L of acetonitrile to give the desired compound 36.

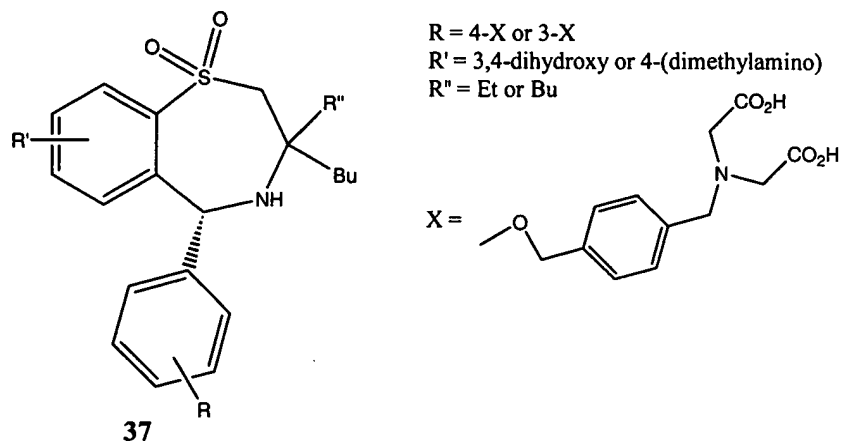
[703] Example 19A

[704] Compound 36 also can be prepared in accordance with an alternative synthetic scheme illustrated below in Scheme III:

0991333.072501



[705] Example 20



[706] Step 1: Preparation of chlorobenzyl intermediate

[707] To a stirred solution of 144 mg (3.59 mmol, 60% dispersion) of sodium hydride in 29 mL of dimethylformamide is added 3.26 mmol of 15, 16, 19, 20, 21, 22, 23 or 24 (obtained from Example 6 or 7), and the resulting solution is stirred at ambient temperature for 45 minutes. To the solution is added 7.13 g (40.75 mmol) of dichloro-p-xylene, and the mixture is stirred overnight. The dimethylformamide is removed *in vacuo* and the residue is extracted with ethyl acetate and washed with brine. The extract is dried over magnesium sulfate and concentrated *in vacuo* to give a chlorobenzyl intermediate.

[708] Step 2: Preparation of amino diester

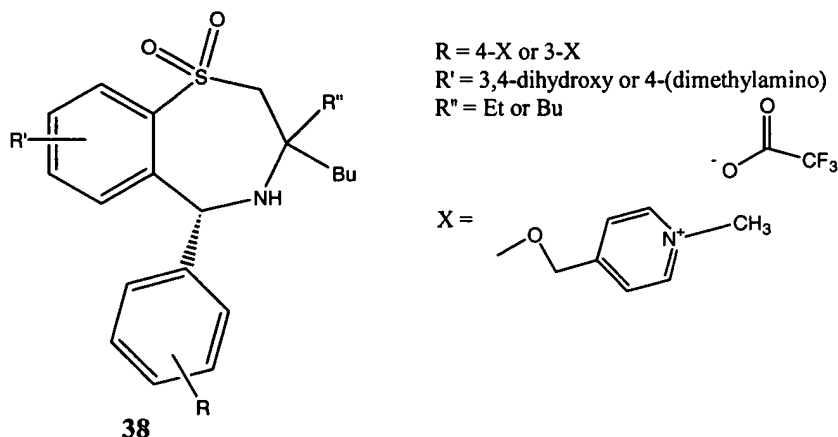
[709] A mixture of 1.72 mmol of the chlorobenzyl intermediate (obtained from Step 1), 1.63 g (8.6 mmol) of diethylaminodiacetate, and 0.72 g (8.6 mmol) of sodium bicarbonate in 30 mL of dimethylformamide is stirred at 100°C for 6 hours. The dimethylformamide is removed *in vacuo* and the residue is extracted with ether and washed with brine. The extract is dried over magnesium sulfate and the concentrated residue is purified by column chromatography to give an amino diester intermediate. For reactions with reagents 21, 22, 23 or 24, removal of the acetone protecting group is accomplished by dissolving the substrate in 4:1 tetrahydrofuran/water at 0°C, adding excess trifluoroacetic acid, and stirring at room temperature overnight. The

reaction is neutralized with ammonium hydroxide, and the tetrahydrofuran removed under reduced pressure. The product is then extracted into ethyl acetate and concentrated *in vacuo* to give a diester intermediate. See, e.g., Y. Leblanc et al., *J. Org. Chem.*, **51**, 189-93 (1986).

[710] Step 3: Preparation of amino diacid

[711] A solution of 1.15 mmol of the dibenzyl ester (obtained from Step 2) and 0.232 g (5.52 mmol) of lithium hydroxide in 30 mL of tetrahydrofuran and 30 mL of water is stirred at 40°C under nitrogen for 4 hours. The reaction mixture is diluted with ether and washed with 1% HCl. The aqueous layer is extracted twice with ether, and the combined extracts are washed with brine, dried over magnesium sulfate, and concentrated *in vacuo* to give the desired compound 37.

[712] Example 21



[713] Step 1: Preparation of picolyl intermediate

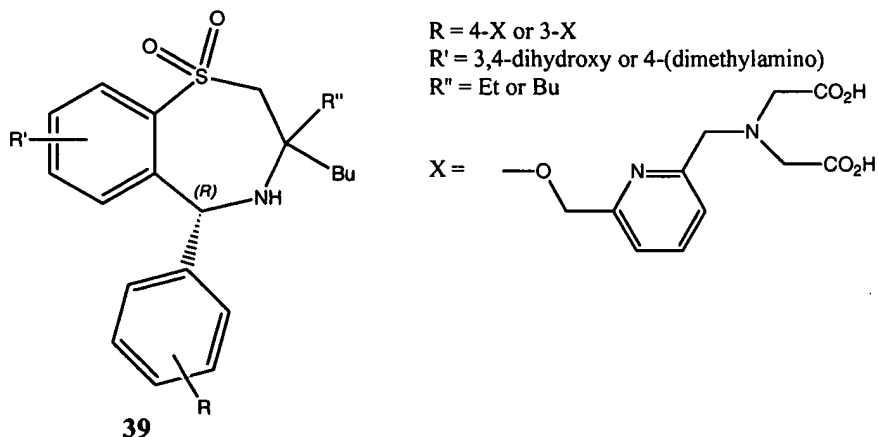
[714] 1.4 g (60% oil dispersion, 35 mmol) of sodium hydride is added to a stirred solution of 26.1 mmol of **15**, **16**, **19**, **20**, **21**, **22**, **23** or **24** (obtained from Example 6 or 7) in 200 mL dimethylformamide. The reaction mixture is stirred at ambient temperature for one hour. A solution of 4-picolyl-chloride hydrochloride is prepared by treating 5.99 g (36.5 mmol) of 4-picolyl chloride hydrochloride with cold saturated sodium bicarbonate solution and extracting the solution with diethyl ether. The ethereal extract is washed with brine, dried over magnesium sulfate, and filtered. The reaction

mixture is then cooled in an ice bath and the solution of 4-picolyl chloride hydrochloride in diethyl ether added. The reaction mixture is stirred at ambient temperature for 17 hours. The reaction mixture is quenched with 25 mL of saturated ammonium chloride and diluted with 600 mL ethyl acetate. It is then washed with 4X250 mL water, washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification by silica gel chromatography (Waters-Delta 500 preparative scale HPLC) using 60% ethyl acetate/hexanes yields a picolyl intermediate.

[715] Step 2: Preparation of quaternary salt

[716] To a stirred solution of 0.74 mmol of the picolyl intermediate (obtained from Step 4) in 10 mL of acetonitrile and 3 mL of methylene chloride, 137 mg (0.97 mmol) of iodomethane is added. The reaction is stirred at ambient temperature for 16 hours and then concentrated under a nitrogen stream. Purification by reversed phase chromatography provides the desired compound **38**. For reactions with reagents **21**, **22**, **23** or **24**, removal of the acetonide protecting group is accomplished by dissolving the substrate in 4:1 tetrahydrofuran/water at 0 °C, adding excess trifluoroacetic acid, and stirring at room temperature overnight. The reaction is neutralized with ammonium hydroxide, and the tetrahydrofuran removed under reduced pressure. Ion exchange with trifluoroacetate anion yields the desired compound **38**. See, e.g., Y. Leblanc et al., *J. Org. Chem.*, **51**, 189-93 (1986).

[717] Example 22



[718] Step 1: Preparation of picolinyl chloride intermediate

[719] Anhydrous K_2CO_3 (0.45 g, 3.2 mmol), tetrabutylammonium iodide (0.1 g, 0.2 mmol) and 2,6-bis(chloromethyl)pyridine (1.2 g, 10.8 mmol) are added to a flask containing a solution of **15**, **16**, **19**, **20**, **21**, **22**, **23** or **24** (2.1 mmol, obtained from Example 6 or 7) in acetone (50 mL). The flask is equipped with nitrogen gas adapter and magnetic stirrer. The reaction mixture is heated to reflux overnight. After 18 hours, the reaction is diluted with ether and washed with water and brine (30 mL). The organic layers are dried over magnesium sulfate, filtered and concentrated *in vacuo*. Chromatographic purification through silica gel, eluting with 25% ethyl acetate/hexane, yields a picolyl chloride intermediate.

[720] Step 2: Preparation of pyridinyl diester intermediate

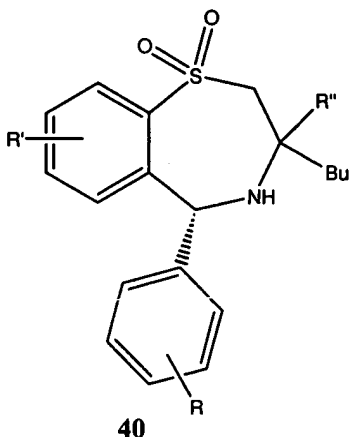
[721] A mixture of diethylaminodiacetate (8 g, 68 mmol) and sodium carbonate (0.63 g, 5.9 mmol) is treated with the picolyl chloride intermediate (1.2 mmol, obtained from Step 1) and the reaction mixture is stirred at 160°C for three hours. The reaction mixture is cooled and diluted with ether and washed with 1% HCl, water (25 mL), and brine (50 mL). The combined extracts are dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue is purified by distillation in a Kugelrohr to provide a pyridinyl diester intermediate. For reactions with reagents **21**, **22**, **23** or **24**, removal of the acetonide protecting group is accomplished by dissolving the substrate in 4:1 tetrahydrofuran/water at 0°C, adding excess trifluoroacetic acid, and stirring at room temperature overnight. The reaction is neutralized with ammonium hydroxide, and the tetrahydrofuran removed under reduced pressure. The product is then extracted into ethyl acetate and concentrated *in vacuo* to give the pyridinyl diester intermediate. See, e.g., Y. Leblanc et al., *J. Org. Chem.*, **51**, 189-93 (1986).

[722] Step 3: Preparation of pyridinyl diacid

[723] A mixture of pyridine-aminodiacetate intermediate (0.93 mmol, obtained from Step 2), and lithium hydroxide monohydrate (0.18 g, 4.5 mmol) in tetrahydrofuran/ water (25.0 mL, 1:1) is stirred at 40 °C overnight (18 hours). The reaction mixture is then diluted with ether and washed with 1% HCl, water (20 mL), and brine (30 mL). The

organic layers are dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the desired compound **39**.

[724] Example 23



R = 4-X or 3-X
 R' = 3,4-dihydroxy or 4-(dimethylamino)
 R'' = Et or Bu
 X = PEG 1000

[725] Step 1: Preparation of monomethyl PEG mesylate intermediate

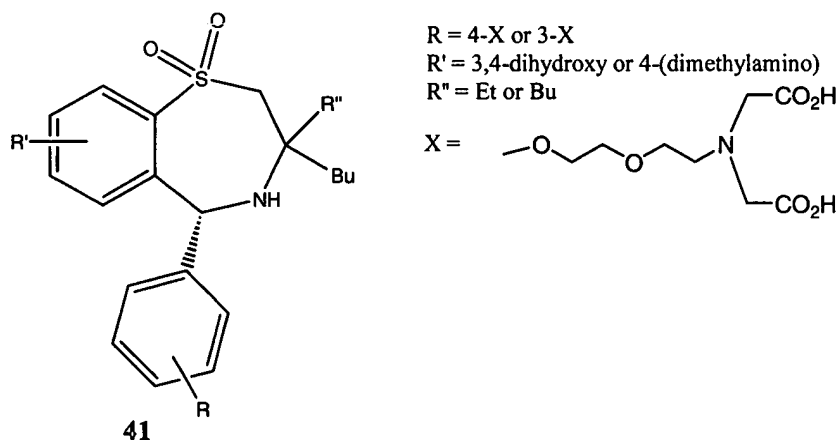
[726] To a solution of 20 g of monomethyl ether PEG in 100 mL of methylene chloride, 2.2 g (22 mmol) of triethyl amine is added. To this solution, 2.5 g (22 mmol) of methanesulfonyl chloride is added dropwise at 0°C. The resulting solution is stirred overnight at ambient temperature. The triethyl amine hydrochloride is filtered off to give a monomethyl PEG mesylate intermediate which is used in the next step without further purification and characterization.

[727] Step 2: Preparation of polyethylene-linked benzothiepine

[728] A mixture of 38 mg (1.52 mmol 95%) of sodium hydride and 1.52 mmol of **15**, **16**, **19**, **20**, **21**, **22**, **23** or **24** (obtained from Example 6 or 7) in 5.5 mL of dimethylformamide is stirred at ambient temperature under nitrogen for 30 minutes. To the solution, 0.55 g (0.51 mmol) of the mesylate PEG intermediate (obtained from Step 1) in 5.5 mL of dimethylformamide is added. The resulting solution is stirred overnight under nitrogen at 50°C. The dimethylformamide is removed *in vacuo* and

the residue extracted with methylene chloride and washed with brine. The extract is then dried over magnesium sulfate and the concentrated residue purified by column chromatography to give the desired compound 40. For reactions with reagents 21, 22, 23 or 24, removal of the acetonide protecting group is accomplished by dissolving the substrate in 4:1 tetrahydrofuran/water at 0°C, adding excess trifluoroacetic acid, and stirring at room temperature overnight. The reaction is neutralized with ammonium hydroxide, and the tetrahydrofuran removed under reduced pressure. The product is then extracted into ethyl acetate and concentrated *in vacuo* to give the desired compound 40. See, e.g., Y. Leblanc et al., *J. Org. Chem.*, **51**, 189-93 (1986).

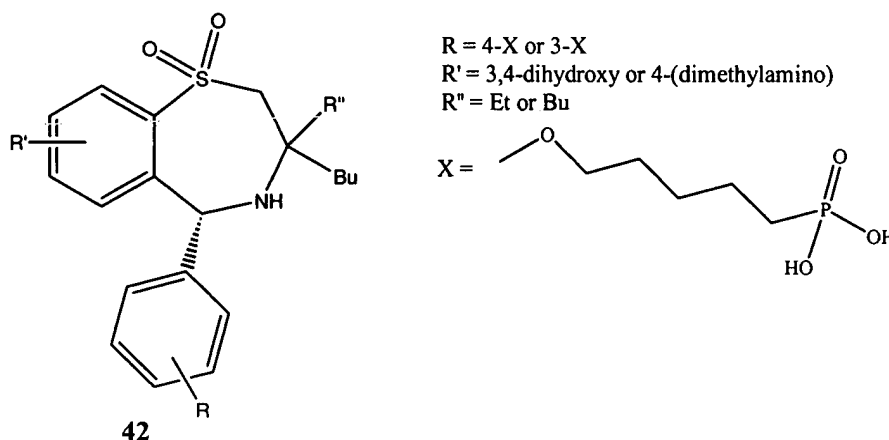
[729] Example 24



[730] A mixture of 10.7 mmol of 15, 16, 19, 20, 21, 22, 23 or 24 (obtained from Example 6 or 7), 11.45 g of diethyliminodiacetate, and 1.14 g of sodium carbonate is held at 160°C for 3.5 hours, diluted with brine and extracted with methylene chloride. The methylene chloride layer is washed with brine, dried (magnesium sulfate) and concentrated in vacuum. The residue is kugelrohr distilled at 0.5 torr at 120°C to remove excess diethyliminodiacetate and to give a residue. A mixture of this residue, 0.8 g of lithium hydroxide, 25 mL of tetrahydrofuran, and 25 mL of water is held at 45°C for 3 days and then concentrated in vacuum to remove the tetrahydrofuran. The residual aqueous solution is diluted with 25 mL of water, acidified to pH 2 and extracted with methylene chloride (2x50 ml). The methylene chloride layer is dried (magnesium sulfate) and concentrated *in vacuo* to give the desired compound 41. For reactions with reagents 21, 22, 23 or 24, removal of the acetonide protecting group is

accomplished by dissolving the substrate in 4:1 tetrahydrofuran/water at 0°C, adding excess trifluoroacetic acid, and stirring at room temperature overnight. The reaction is neutralized with ammonium hydroxide, and the tetrahydrofuran removed under reduced pressure. The product is then extracted into ethyl acetate, and concentrated *in vacuo* to give the desired compound **41**. See, e.g., Y. Leblanc et al., *J. Org. Chem.*, **51**, 189-93 (1986).

[731] Example 25



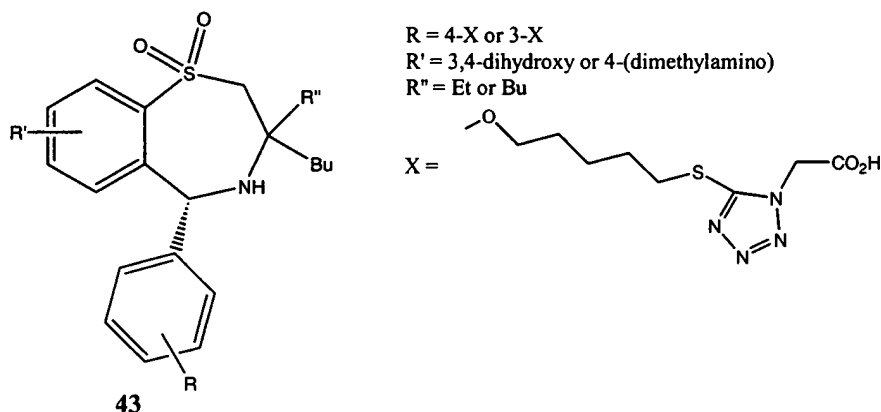
[732] Step 1: Preparation of pentyl bromide intermediate

[733] A solution of **15**, **16**, **19**, **20**, **21**, **22**, **23** or **24** (1.09 mmol, obtained from Example 6 or 7) in 5 mL of dimethylformamide is added via a syringe to a stirred solution of 36 mg of 95% sodium hydride (1.41 mmol) in 5 mL of dimethylformamide at -10°C in an acetone-dry ice bath. The resulting solution is stirred at -10°C for 30 minutes. A solution of 1.25 g of 1,5-dibromopentane (5.45 mmol) in 5 mL of dimethylformamide is then added. The mixture is stirred at -10°C for another 30 minutes and allowed to warm up to room temperature and stirred for 1 hour. The reaction mixture is then quenched with water at 0°C and extracted with ethyl acetate. The ethyl acetate layer is dried over magnesium sulfate and concentrated *in vacuo*. The crude product is chromatographed on silica gel column to give a pentyl bromide intermediate.

[734] Step 2: Preparation of phosphonic acid

[735] A stirred solution of 400 mg of the pentyl bromide intermediate (0.66 mmol, obtained from Step 1) in 2 mL of tris(trimethylsilyl) phosphite is refluxed at 100°C overnight. The reaction mixture is cooled to room temperature and 30 mL of 50% methanol/water solution is added. The reaction mixture is stirred at room temperature for 5 hours. The reaction mixture is concentrated *in vacuo* and the resulting aqueous solution is extracted with methylene chloride. The methylene chloride solution is dried over magnesium sulfate and concentrated *in vacuo* to yield the desired product 42. For reactions with reagents 21, 22, 23 or 24, removal of the acetonide protecting group is accomplished by dissolving the substrate in 4:1 tetrahydrofuran/water at 0°C, adding excess trifluoroacetic acid, and stirring at room temperature overnight. The reaction is neutralized with ammonium hydroxide, and the tetrahydrofuran removed under reduced pressure. The product is then extracted into ethyl acetate and concentrated *in vacuo* to give the desired product 42. See, e.g., Y. Leblanc et al., *J. Org. Chem.*, 51, 189-93 (1986).

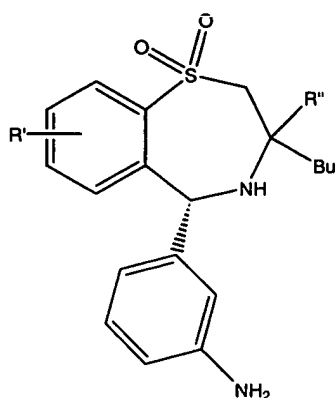
[736] Example 26



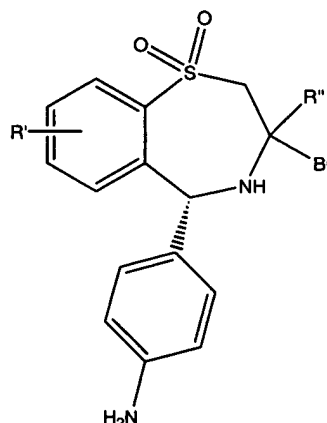
[737] A mixture of 0.325 g (1.78 mmol) of 5-mercaptopentazolateacetic acid sodium salt, 1.0 g of potassium carbonate, and 30 mL of dimethylformamide is stirred for 2 hours and then charged with 1.74 mmol of the pentyl bromide intermediate (Example 13, Step 1). The reaction mixture is stirred for 20 hours at room temperature and concentrated in vacuum. The residue is then stirred in ether and water (100 mL each). The resulting precipitate is combined with the aqueous layer, acidified with concentrated

HCl and extracted with methylene chloride. The methylene chloride layer is dried (magnesium sulfate) and concentrated *in vacuo* to yield the desired product 43. For reactions with reagents 21, 22, 23 or 24, removal of the acetonide protecting group is accomplished by dissolving the substrate in 4:1 tetrahydrofuran/water at 0°C, adding excess trifluoroacetic acid, and stirring at room temperature overnight. The reaction is neutralized with ammonium hydroxide, and the tetrahydrofuran removed under reduced pressure. The product is then extracted into ethyl acetate, and concentrated *in vacuo* to give the desired product 43. See, e.g., Y. Leblanc et al., *J. Org. Chem.*, **51**, 189-93 (1986).

[738] Example 27



- 44, R' = 3,4-acetonide, R'' = Et
 45, R' = 4-(dimethylamino), R'' = Et
 46, R' = 3,4-acetonide, R'' = Bu
 47, R' = 4-(dimethylamino), R'' = Bu



- 44a, R' = 3,4-acetonide, R'' = Et
 45a, R' = 4-(dimethylamino), R'' = Et
 46a, R' = 3,4-acetonide, R'' = Bu
 47a, R' = 4-(dimethylamino), R'' = Bu

[739] Step 1: Preparation of triflic intermediate

[740] Triflic anhydride (4.1 mL, 24.4 mmol, 1.1 equivalents) is added dropwise to a solution of 22.13 mmol of compound 15, 16, 19, 20, 21, 22, 23 or 24 (obtained from Example 6 or 7) in pyridine (42 mL) at 0°C under nitrogen gas. Upon completion of the triflic anhydride addition, the bath is removed and the reaction stirred at room temperature for 21 hours. The pyridine is removed *in vacuo* and the resulting oil is taken up in water (100 mL) and extracted three times with ethyl acetate (45 mL each). The combined organics are washed with 10% CuSO₄ (100 mL) and brine (100 mL),

and then dried over magnesium sulfate, filtered and the solvent evaporated. The residue is purified by chromatography on silica gel to give a triflic intermediate.

[741] Step 2: Preparation of imine intermediate

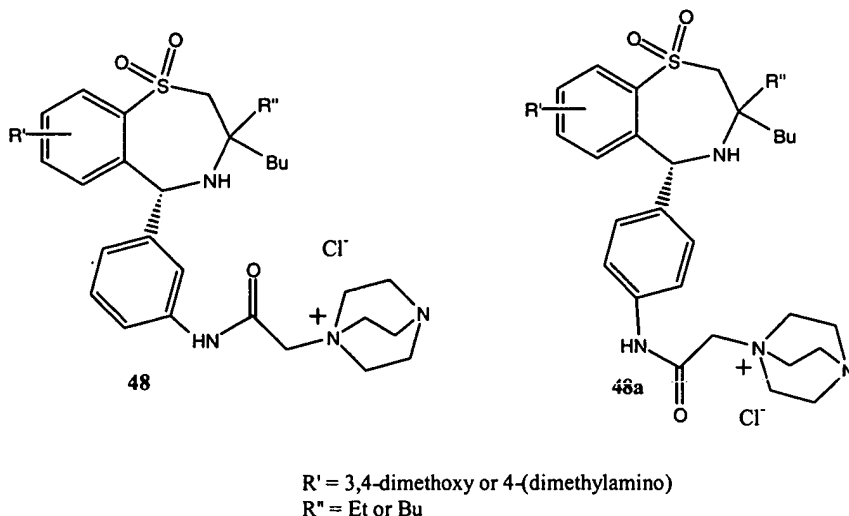
[742] To a solution of 19.28 mmol of the triflate intermediate (prepared in Step 1), palladium (II) acetate (433 mg, 1.93 mmol, 10 mol%), racemic 2,2'-bis-(biphenylphosphanyl)-1,1'-binaphthyl (1.41 g, 2.26 mmol, 12 mol%) and cesium carbonate (8.86 g, 27.2 mmol, 2.0 equivalents) in 114 mL of tetrahydrofuran is added 6.6 mL of benzophenone imine (39.4 mmol, 2.0 equivalents). The mixture is stirred at reflux for 4 hours, filtered through celite and the solvent removed *in vacuo* providing an imine intermediate.

[743] Step 3: Preparation of aniline

[744] To a solution of 19.3 mmol of the crude imine intermediate (prepared in Step 2) in methanol (200 mL) is added sodium acetate (6.33 g, 77.2 mmol, 4 equivalents) and hydroxylamine hydrochloride (4.02 g, 57.9 mmol, 3 equivalents). The mixture is stirred for 1 hour and 1N sodium bicarbonate (100 mL) is added. The mixture is then extracted with methylene chloride (2 X 100 mL, 1 X 50 mL). The combined organics are washed with brine (100 mL), dried over magnesium sulfate, filtered and the solvent evaporated. The residue is purified by chromatography on silica gel to afford the desired aniline 44, 44a, 45, 45a, 46, 46a, 47 or 47a.

09012233 072501
105220 EE22T660

[745] Example 28



[746] Step 1: Preparation of chloroacetyl intermediate

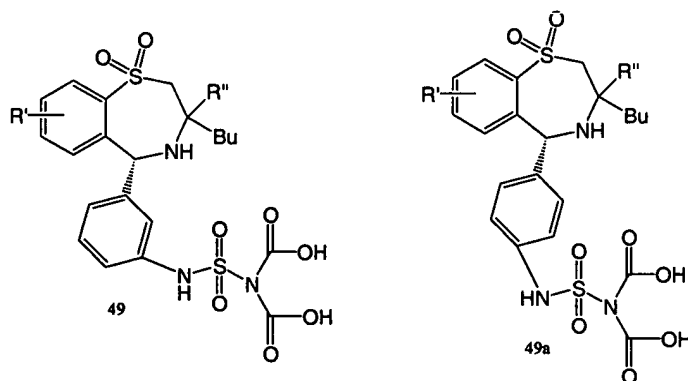
[747] A solution of **44**, **44a**, **45**, **45a**, **46**, **46a**, **47** or **47a** (2.2 mmol, obtained from Example 27) in methylene chloride (10 mL) at 0°C under nitrogen is treated with N,N-diisopropyl-ethylamine (0.53 mL, 3.1 mmol, 1.4 equivalents), followed by the dropwise addition of chloroacetyl chloride (0.21 mL, 2.6 mmol, 1.2 equivalents) over a 10 minute period. The reaction mixture is stirred and allowed to warm to 25°C over a 2 hour period. The mixture is quenched by the addition of 1N HCl (25 mL) and the aqueous layer is extracted with ethyl acetate (2 x 25 mL). The combined organic extracts are washed with saturated aqueous sodium bicarbonate (2 x 25 mL) and brine (30 mL), and then dried (magnesium sulfate) and concentrated to give a chloroacetyl intermediate.

[748] Step 2: Preparation of quaternary salt

[749] A solution of the chloroacetyl intermediate (0.05 mmol, obtained from step 1) in acetonitrile (1 mL) at 50°C under nitrogen is treated with diazabicyclo[2.2.2]octane (10 mg, 0.09 mmol, 1.8 equivalents) and stirred at 50°C for 2 hours. The reaction

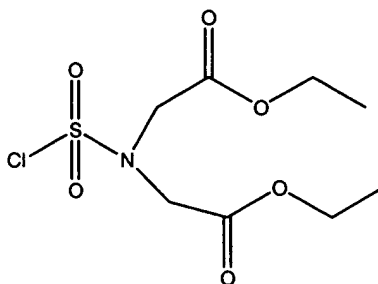
mixture is allowed to cool to 25°C and then concentrated to form a residue. The residue is dissolved in warm acetonitrile and *tert*-butyl methyl ether is added. The mixture is allowed to stand overnight to precipitate the desired compound **48** or **48a**. For reactions with reagents **21**, **22**, **23** or **24**, removal of the acetonide protecting group is accomplished by dissolving the substrate in 4:1 tetrahydrofuran/water at 0°C, adding excess trifluoroacetic acid, and stirring at room temperature overnight. The reaction is neutralized with ammonium hydroxide, and the tetrahydrofuran removed under reduced pressure. Ion exchange with chloride ion will give the desired product **48** or **48a**. See, e.g., Y. Leblanc et al., *J. Org. Chem.*, **51**, 189-93 (1986).

[750] Example 29



R' = 3,4-dimethoxy or 4-(dimethylamino)
R'' = Et or Bu

[751] Step 1: Preparation of the sulfonamoyl chloride intermediate



[752] Sulfuryl chloride (27.552 g/204.1 mmol) and chloroform (50.0 mL) are combined in a 250 mL round-bottom flask. The reaction flask is purged with nitrogen, equipped with a magnetic stirrer, and cooled to 0°C. A solution of diethyl iminodiacetate (18.902 g/99.9 mmol) and triethylamine (10.112 g/99.9 mmol) is added dropwise

while maintaining the temperature of the solution below 20°C. After the addition is complete, the reaction mixture is allowed to warm to room temperature. After 2 hours, the reaction mixture is poured into ice water (100 mL) and mixed well. The organic layer is separated, washed with 10% aqueous HCl (50 mL) and chilled water (2 x 50 mL), dried (CaCl₂), filtered, and concentrated *in vacuo* to give a sulfonamoyl chloride intermediate as an amber liquid (5.706 g/20%).

[753] Step 2: Preparation of the diester intermediate

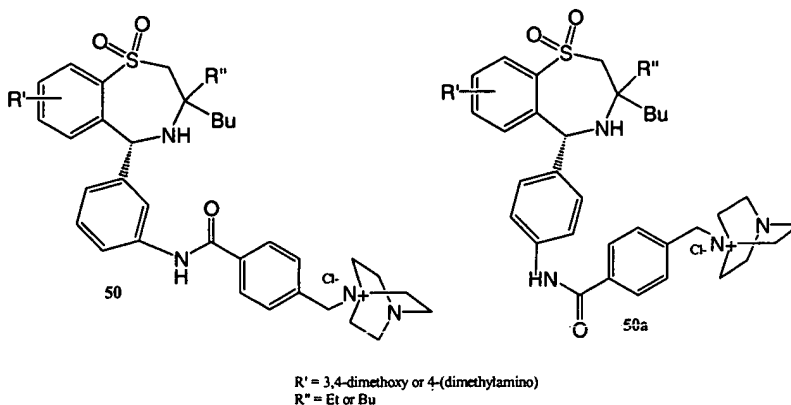
[754] The 3-aminobenzothiepine **44**, **44a**, **45**, **45a**, **46**, **46a**, **47** or **47a** (1.097 mmol, obtained from Example 27), toluene (5.00 mL), diisopropylethylamine (0.148 g/1.148 mmol), and the sulfonamoyl chloride intermediate (0.650 g/2.260 mmol, obtained from step 1) are combined in a 25 mL round-bottom flask. The reaction flask is purged with nitrogen and equipped with magnetic stirrer. After 24 hours, methylene chloride (75.0 mL) is added. The mixture is washed with aqueous sodium bicarbonate (25.0 mL) and then aqueous sodium chloride (25.0 mL), dried (magnesium sulfate), and concentrated *in vacuo*. Purifying by flash chromatography on silica gel eluting with ethyl acetate/hexane and concentrating *in vacuo* gives a diester intermediate.

[755] Step 3: Preparation of diacid

[756] The diester intermediate (0.316 mmol, obtained from step 2) and tetrahydrofuran (1.00 mL) are combined in a 10 mL round-bottom flask. The reaction flask is purged with nitrogen and equipped with magnetic stirrer. A solution of LiOH·H₂O (0.030 g/0.715 mmol) in water (0.50 mL) is added. After 4 hours, additional LiOH·H₂O (0.015 g/0.357 mmol) is added. After 30 minutes, water (6.0 mL) is added. The aqueous mixture is washed with diethyl ether (4 x 4.0 mL), and acidified with aqueous 3.0 N HCl (0.40 mL). The product precipitates and is filtered, washed with water (2.0 mL), and concentrated *in vacuo*. Precipitation from acetonitrile/diethyl ether/hexanes gives the desired product **49** or **49a**. For reactions with reagents **21**, **22**, **23** or **24**, removal of the acetonide protecting group is accomplished by dissolving the substrate in 4:1 tetrahydrofuran/water at 0°C, adding excess trifluoroacetic acid, and stirring at room temperature overnight. The reaction is neutralized with ammonium

hydroxide, and the tetrahydrofuran removed under reduced pressure. Precipitation from acetonitrile/diethyl ether/hexanes gives the desired product **49** or **49a**. See, e.g., Y. Leblanc et al., *J. Org. Chem.*, **51**, 189-93 (1986).

[757] Example 30



[758] Step 1: Preparation of chlorobenzoyl intermediate

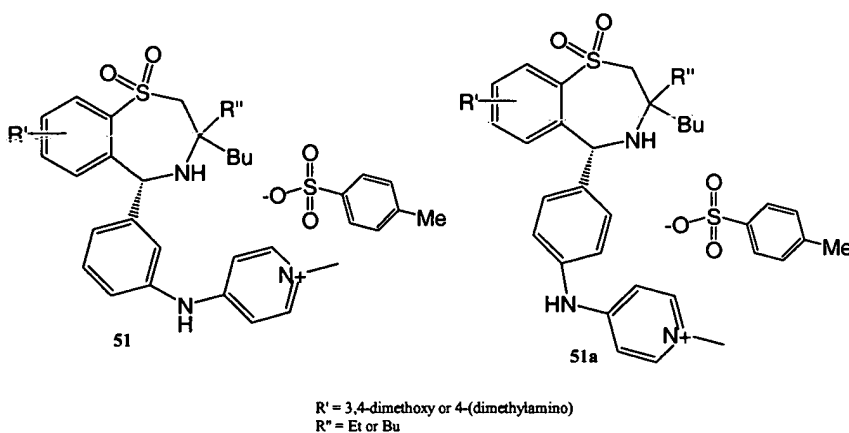
[759] A solution of the 3-aminobenzothiepine **44**, **44a**, **45**, **45a**, **46**, **46a**, **47** or **47a** (2.2 mmol, obtained from Example 27) in methylene chloride (10 mL) at 0°C under nitrogen is treated with N,N-di-isopropyl-ethylamine (0.53 mL, 3.1 mmol, 1.4 equivalents), followed by the dropwise addition of 4-chlorobenzoyl chloride (0.455 g, 2.6 mmol, 1.2 equivalents) over a 10 minute period. The reaction mixture is stirred and allowed to warm to 25°C over a 2 hour period. The mixture is quenched by the addition of aqueous ammonium chloride and the aqueous layer is extracted with ethyl acetate (2 x 25 mL). The combined organic extracts are washed with saturated aqueous sodium bicarbonate (2 x 25 mL) and brine (30 mL), and then dried (magnesium sulfate) and concentrated to give a chlorobenzoyl intermediate.

[760] Step 2: Preparation of quaternary salt

[761] A solution of the chlorobenzoyl intermediate (0.05 mmol, obtained from step 1) in acetonitrile (1 mL) at 50°C under nitrogen is treated with diazabicyclo[2.2.2]octane (10 mg, 0.09 mmol, 1.8 equivalents) and stirred at 50°C for 2 hours. The reaction mixture is allowed to cool to 25°C and then concentrated *in vacuo* to give the desired compound **50** or **50a**. For reactions with reagents **21**, **22**, **23** or **24**, removal of the

[illegible]

[762] Example 31



[763] Step 1: Preparation of pyridyl intermediate

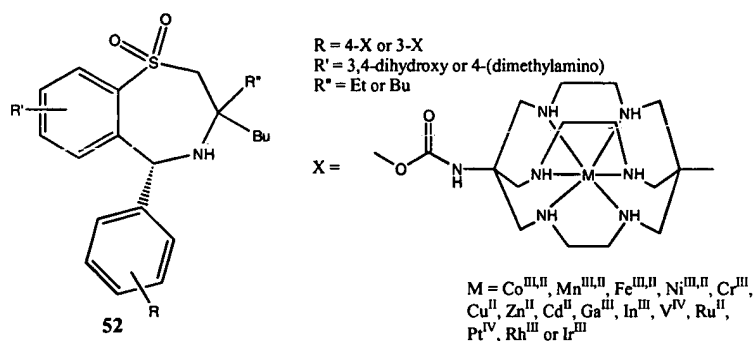
[764] A solution of the 3-aminobenzothiepine **44**, **44a**, **45**, **45a**, **46**, **46a**, **47** or **47a** (4.37 mmol, obtained from Example 26) in ethanol (14.0 mL) under nitrogen is treated with 4-bromopyridine hydrochloride (1.041 g, 5.35 mmol) and heated to reflux. After 48 hours, the reaction mixture is cooled to room temperature and concentrated *in vacuo*. The residue is dissolved in ethyl acetate (150 mL) and washed with aqueous sodium bicarbonate (2 x 70 mL) and brine (50 mL). The mixture is dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residue is purified by flash chromatography on silica gel to give a pyridyl intermediate.

[765] Step 2: Preparation of quaternary salt

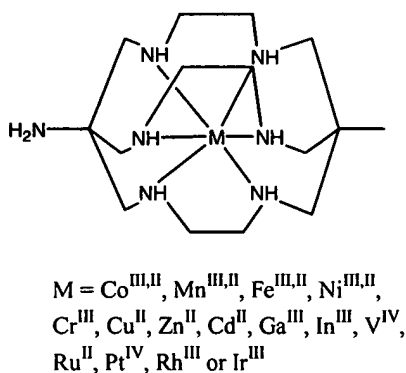
[766] A solution of the pyridyl intermediate (3.39 mmol, obtained from step 1) in acetonitrile (18.0 mL) at room temperature under nitrogen is treated with methyl p-toluenesulfonate (0.550 mL, 3.77 mmol) and stirred for 17 hours. The reaction

mixture is filtered and concentrated to give the desired compound **51** or **51a**. For reactions with reagents **21**, **22**, **23** or **24**, removal of the acetonide protecting group is accomplished by dissolving the substrate in 4:1 tetrahydrofuran/water at 0°C, adding excess trifluoroacetic acid, and stirring at room temperature overnight. The reaction is neutralized with ammonium hydroxide, and the tetrahydrofuran removed under reduced pressure. Ion exchange with tosylate anion will give the desired product **51** or **51a**. See, e.g., Y. Leblanc et al., *J. Org. Chem.*, **51**, 189-93 (1986).

[767] Example 32



[768] Step 1: Preparation of the metal cage complex



[769] A metal cage complex is prepared as described in A.M. Sargeson et al, *J. Chem. Soc., Chem Commun.*, 1844-1846 (1993).

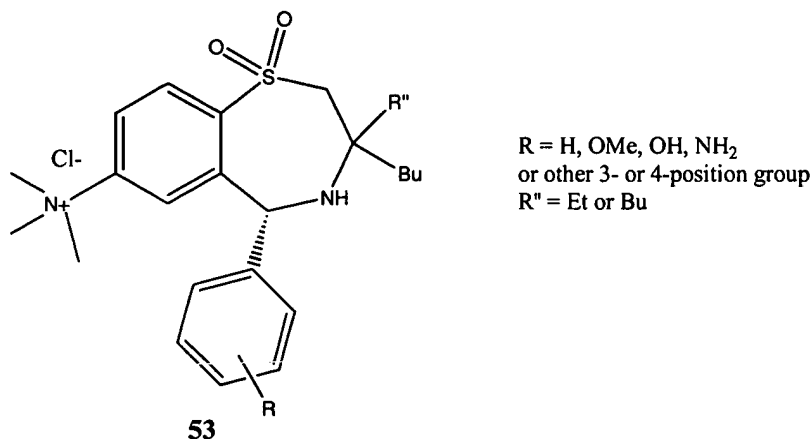
[770] Step 2: Preparation of the carbamoyl chloride intermediate

[771] The metal cage complex (2.00 mmol, obtained from Step 1) is combined with methylene chloride (15.0 mL), triethylamine (0.223 g/ 2.20 mmol) and phosgene (0.218 g/ 2.20 mmol) in a dry 25 mL round-bottom flask. After stirring overnight at room temperature, the reaction mixture is concentrated *in vacuo*. The residue is triturated with tetrahydrofuran (5 mL), filtered and concentrated *in vacuo* to give a carbamoyl chloride intermediate. See, e.g., *Tetrahedron Lett.*, **39**, 757-760 (1998).

[772] Step 3: Preparation of the carbamate

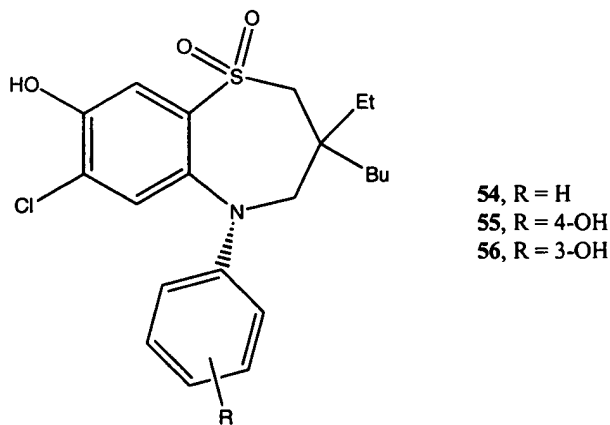
[773] The hydroxybenzothiepine **15**, **16**, **19**, **20**, **21**, **22**, **23** or **24** (0.828 mmol, obtained from Example 6 or 7), triethylamine (0.100 g/ 0.994 mmol) and toluene (1.0 mL) are combined in a 10 mL round-bottom flask. The reaction flask is purged with nitrogen, equipped with a magnetic stirrer, and cooled to 0°C. A solution of the carbamoyl chloride (12% in tetrahydrofuran/1.10 mmol, obtained from Step 2) is added. After 3.5 hours, the mixture is filtered and concentrated *in vacuo* to give the desired carbamate **52**. See, e.g., *Tetrahedron Lett.*, **39**, 757-760 (1998). For reactions with reagents **21**, **22**, **23** or **24**, removal of the acetonide protecting group is accomplished by dissolving the substrate in 4:1 tetrahydrofuran/water at 0°C, adding excess trifluoroacetic acid, and stirring at room temperature overnight. The reaction is neutralized with ammonium hydroxide, and the tetrahydrofuran removed under reduced pressure. The product is then extracted into ethyl acetate, and concentrated *in vacuo* to give the diester intermediate. See, e.g., Y. Leblanc et al., *J. Org. Chem.*, **51**, 189-93 (1986).

[774] Example 33



[775] A solution of any corresponding dimethylamino analog of the desired product **53** (0.34 mmol, obtained by suitable modification of the Synthetic Examples of patent application WO96/01844 and the Examples of the present application) in acetonitrile (7.0 mL) at 50°C under nitrogen is treated with methyl iodide (20 equivalents) and stirred for 72 hours. The reaction mixture is concentrated to form a residue. The product is then dissolved in acetonitrile and precipitated with ethyl ether. Ion exchange with chloride ion gives the desired compound **53**.

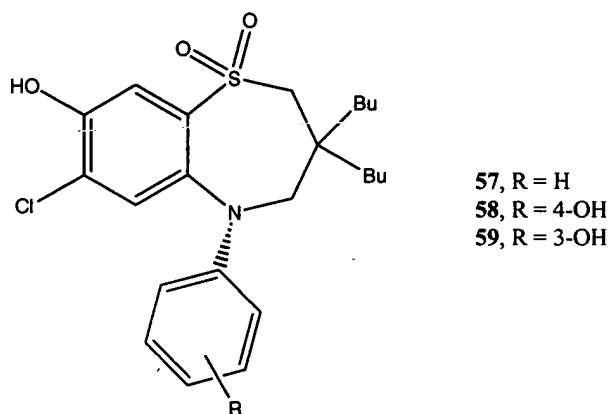
[776] Example 34



[777] Benzothiazepine **54** is prepared as described in steps 1 through 9 of Synthetic Example 1 of patent application WO 99/35135, except that 4-iodoanisole (or 3-iodoanisole) is substituted for iodobenzene in step 7 to give Compound **55** (or Compound **56**).

[778]

[779] Example 35



[780] Step 1: Preparation of 2-(bromomethyl)-2-butyl-hexanoic acid

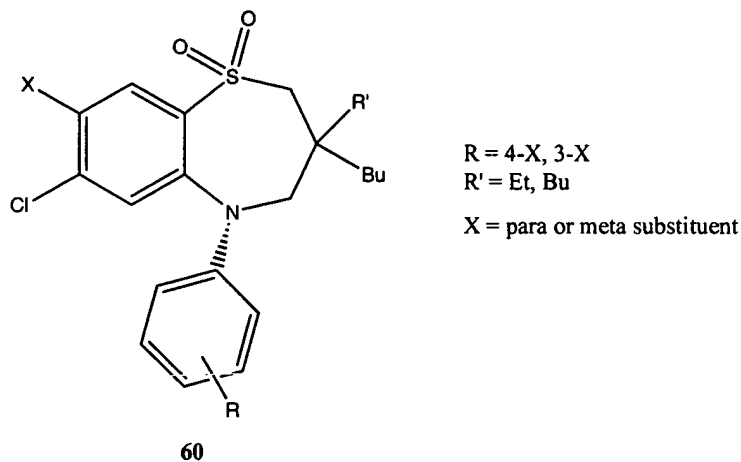
[781] 2-(Bromomethyl)-2-butyl-hexanoic acid is prepared in accordance with the procedure set forth in steps (1) and (2) of Synthetic Example 1 of patent application WO 99/35135, except that 2,2-dibutyl-1,3-propanediol is substituted for 2-butyl-2-ethyl-1,3-propanediol in step 1 of Synthetic Example 1, step 1. 2,2-Dibutyl-1,3-propanediol is prepared, for example, as set forth at column 264 of U.S. Patent 5,994,391.

[782] Step 2: Preparation of butyl-butyl benzothiazepine

[783] Compounds **57**, **58** and **59** are prepared in accordance with the procedure set forth in steps (1) through (9) of Synthetic Example 1 of patent application WO99/35135, except that (a) 2-(bromomethyl)-2-butyl-hexanoic acid (obtained from Step 1) is substituted for 2-(bromomethyl)-2-ethyl-hexanoic acid in step 3 of Synthetic Example 1, and either 4-iodoanisole (for Compound **58**) or 3-iodoanisole (for Compound **59**) is

optionally substituted for iodobenzene (for Compound 57) in step 7 of Synthetic Example 1.

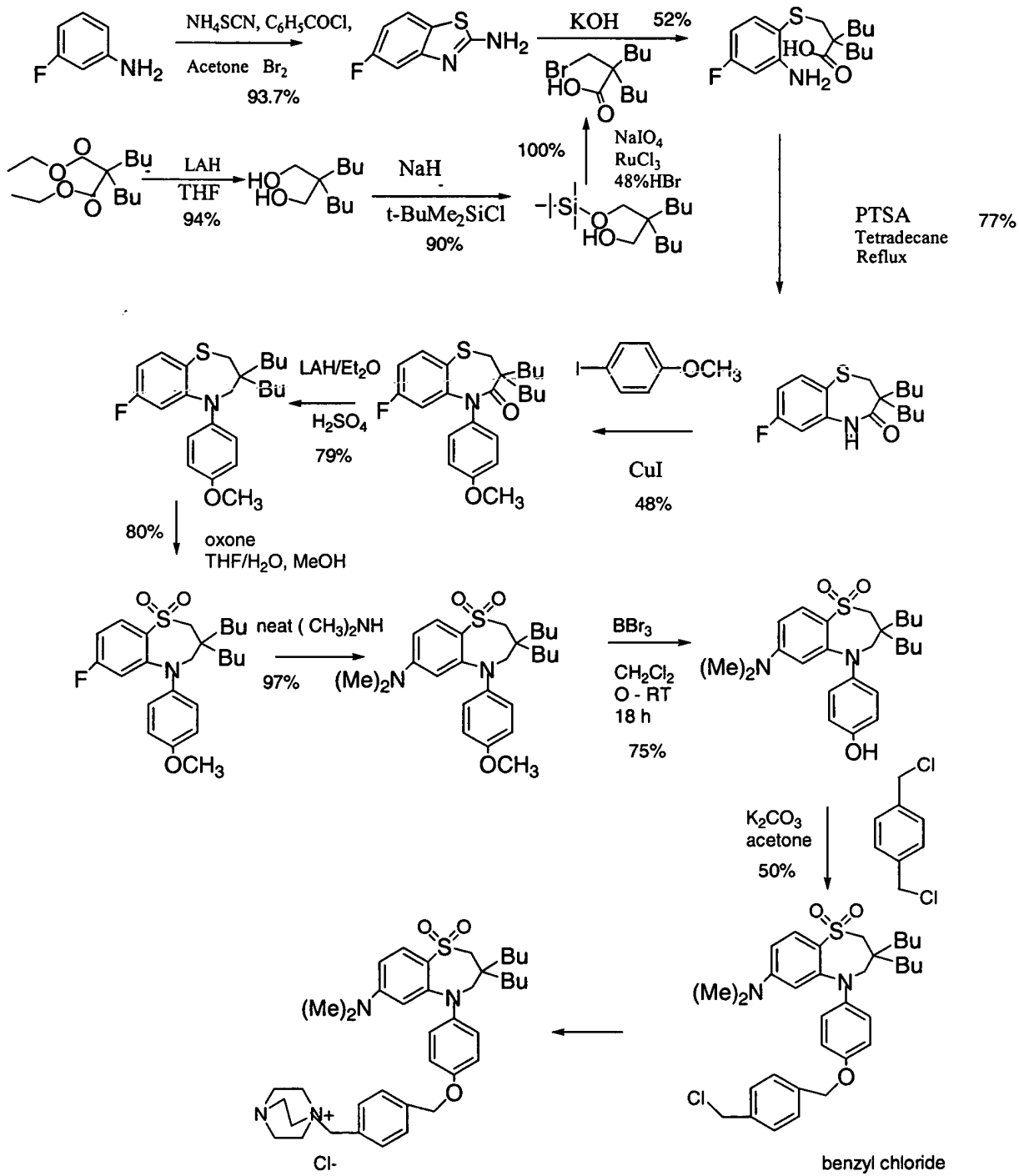
[784] Example 36



[785] Compound 60 comprising a wide variety of R substituents can be prepared by appropriate modification of the procedures described in the above Examples starting with one of compounds 53, 54, 55 and 56 (obtained from Examples 33 and 34).

[786] Similarly, additional 1,5-benzothiazepines can be prepared by appropriate modification of the procedures described in the above Examples. For example, the preparation of the 1,5-benzothiazepine counterpart to 1,4-benzothiazepine 36 described in Examples 19 and 19A can be prepared as illustrated in Scheme IV below:

SCHEME IV



[787] Additional Examples

[788] General Comments

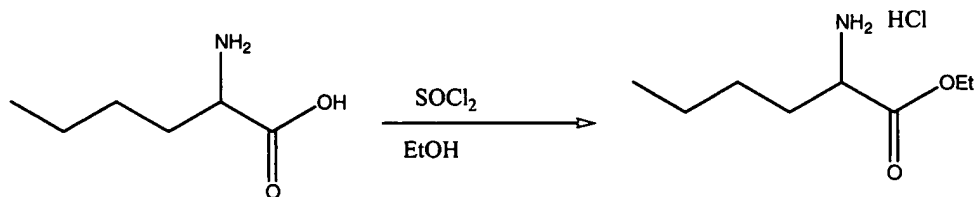
[789] Chemicals were obtained from Aldrich Chemical Company and were used without further purification. ^1H and ^{13}C NMR spectra were recorded on a Varian 300 spectrometer at 300 and 75 MHz respectively. The ^1H chemical shifts are reported in ppm downfield from Me_4Si . The ^{13}C chemical shifts are reported in ppm relative to the center line of CDCl_3 (77.0 ppm). High Resolution Mass spectra were determined by Monsanto Analytical Sciences Center and microanalyses were performed by Atlantic Microlab Inc. HPLC data was obtained on a Spectra Physics 8800 Chromatograph using a Beckman Ultrasphere C18 250 x 4.6 mm column. HPLC conditions: detector wavelength = 254 nm, sample size = 10 μL , flowrate = 1.0 mL/min, mobile phase = (A) 0.1% aqueous trifluoroacetic acid : (B) acetonitrile.

[790] HPLC Gradient:

[791]	Time	%A	%B
[792]	0 min	85	15
[793]	20 min	0	100

[794] Synthesis of the 1,4 benzothiazepines Scheme III

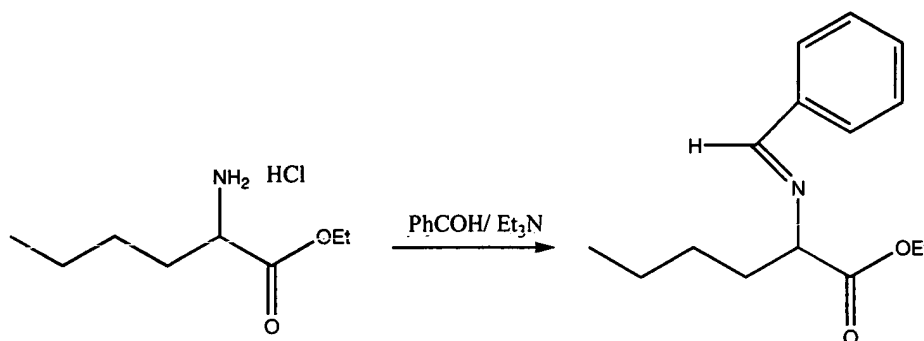
[795] Ethyl 2-aminohexanoate Hydrochloride



[796] A slurry of DL-norleucine (75.0 g, 572 mmol) in absolute ethanol (400 ml) was stirred under nitrogen in an ice-water bath and thionyl chloride (71.4g, 43.8 ml) was added dropwise. The reaction was stirred overnight at 0°C and then gradually warmed to room temperature. The resulting slurry was heated under reflux for 3

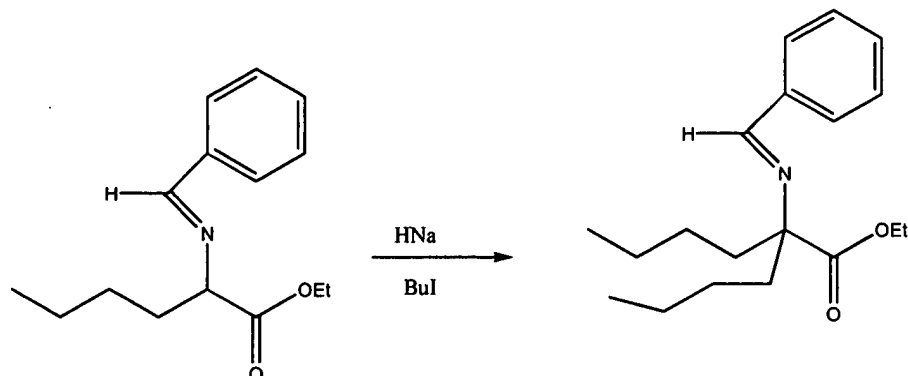
hours. After cool down, the reaction mixture was concentrated to yield desired product (108.9 g/97%) as a light yellow solid. ^1H NMR (D_2O) δ 0.80 (t, J = 7.2 Hz, 3H), 1.20 (t, J = 6.9 Hz, 3H), 1.20-1.36 (m, 4H), 1.84 (m, 2H), 4.02 (t, J = 6.3 Hz, 1H), 4.21 (q, J = 7.4 Hz, 2H). LC/MS (ES/M + H): 160.0.

[797] Ethyl 2-benzylideneamino hexanoate



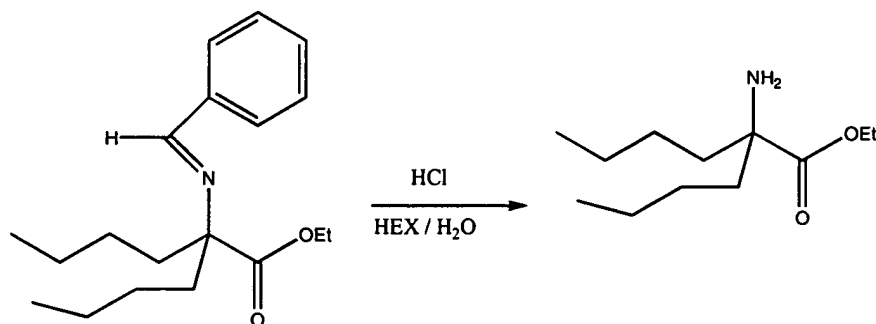
- [798] A solution of the product ethyl 2-amino hexanoate hydrochloride (from the step 1) (108 g, 552 mmol) in CH_2Cl_2 (1200 ml) and MgSO_4 (66.45 g) was stirred at room temperature under nitrogen for 20 minutes. Then, Et_3N (152 ml) was added. After stirring for another 30 minutes, xs. benzaldehyde was added dropwise. The reaction mixture was stirred at room temperature for 2 hours. MgSO_4 (66.5 g) was added and the reaction mixture was heated to reflux for 3 hours. After cool to room temperature, the reaction mixture was stirred overnight, filtered and concentrated. The resulting mixture was triturated in diethyl ether, filtered and concentrated to yield product as a yellow oil (125 g/92%). ^1H NMR (CDCl_3) δ 0.90 (t, J = 6.3 Hz, 3H), 1.27 (t, J = 7.4 Hz, 3H), 1.25-1.38 (m, 4H), 1.83-2.05 (m, 2H), 3.95 (t, J = 6.9 Hz, 1H), 4.21 (q, J = 7.2 Hz, 2H), 7.40 (m, 3H), 7.78 (d, J = 8.1 Hz, 2H), 8.26 (s, 1H). LC/MS (ES/M + H): 248.1.

[799] Ethyl 2-benzylideneamino-2-butylhexanoate



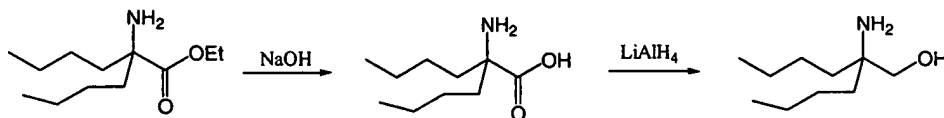
- [800] Sodium hydride (20.23g, 60% dispersion in oil) and DMF (500 ml) were stirred under nitrogen at room temperature for 10 minutes. A solution of the product of ethyl 2-benzylideneamino-2-butylhexanoate in 100 ml DMF was added dropwise. After 2 hours stirring at room temperature, a solution of BuI (102g, 1.1eq) in 50ml of DMF was added dropwise and the reaction left stirring for overnight. The reaction mixture was poured into an ice cold mixture of water (350 ml) , ether (300 ml) and ammonium chloride (74g). The resulting organic layer was dried over potassium carbonate then concentrated to give the desired product as a yellow oil (138.75g, yield = 90.5%). ¹H NMR (CDCl₃) δ 0.90 (t, J = 6.9 Hz, 6H), 1.20-1.40 (m, 8H), 1.28 (t, J = 7.5 Hz, 3H), 1.80-2.00 (m, 4H), 4.22 (q, J = 6.9 Hz, 2H), 7.40 (m, 3H), 7.78 (m, 2H), 8.32 (s, 1H).

[801] Ethyl 2-amino-2-butylhexanoate



[802] The product of ethyl 2-benzylideneamino-2-butylhexanoate was partitioned between hexane and 10% aq. HCl and stirred at room temperature for 2 hours. The aqueous layer was extracted twice with hexane (2 x 100ml). The aqueous layer was added 200 ml of ethyl acetate and was chilled with an ice-water bath. Sodium hydroxide pellets were added to the mixture until the aqueous layer was at pH < 10. After separation, the aqueous layer was extracted twice with EtOAc (2 x 100 ml). The combined EtOAc layers were dried over potassium carbonate, filtered and concentrated to give product as a colorless oil (47.1g, yield 48.08%). ¹H NMR (CDCl₃) δ 0.89 (t, J = 6.9 Hz, 6H), 1.23-1.38 (m, 6H), 1.28 (t, J = 7.5 Hz, 3H), 1.45-1.77 (m, 6H), 4.15 (q, J = 7.2 Hz, 2H). ¹³C NMR (CDCl₃) δ 13.9, 14.3, 23.0, 26.0, 39.9, 60.7, 60.9, 177.4.

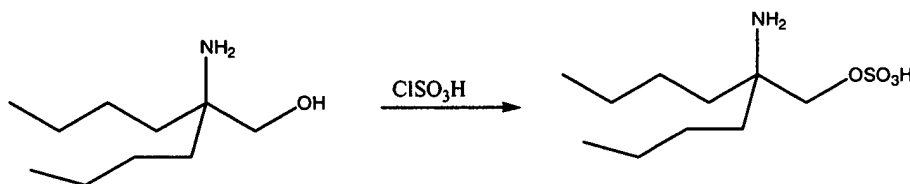
[803] 2-Amino-2-butylhexan-1-ol



[804] To a 1000 ml flask was added ethyl 2-amino -2-butylhexanoate (46g), MeOH (500 ml) and water (200ml). After adding NaOH (9.0 g), the reaction mixture was heated to reflux for 4 hours and then evaporated off solvent to give mixture of sodium 2-amino-2-butylhexanoate and sodium hydroxide. ^1H NMR (D_2O) δ 0.78 (t, J = 6.9 Hz, 6H), 1.05-1.36 (m, 8H), 1.70-1.88 (m, 4H). ^{13}C NMR. LC/MS (ES/M + H): 188.2.

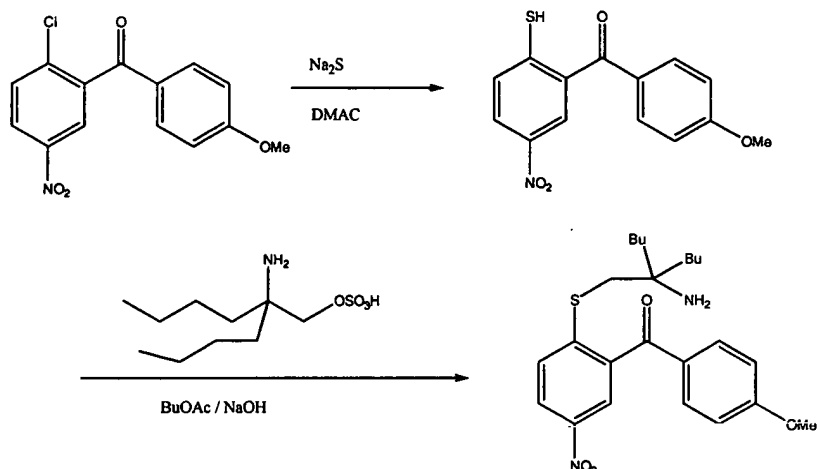
[805] The solid mixture was added to a 1M solution of LiAlH_4 (223 ml, 1.05 eq.) in THF. After complete addition, the reaction mixture was refluxed for 3 hours, then stirred overnight at room temperature. The mixture was cooled to about 0 °C, then quenched with water (100ml) and 1 N aq. NaOH (100 ml). The resulting solid was broke up with additional water (100 ml) and the suspension was heated at 65°C for 10 minutes. After cooling to room temperature, diethyl ether (500 ml) was added, the mixture was stirred and filtered. The diethyl ether layer was separated, dried and concentrated in vacuo to give desired product as a solid. (31.0 g, yield 83.75%). ^1H NMR (CDCl_3) δ 0.84 (t, J = 5.1 H, 6H), 1.10-1.38 (m, 12H), 3.24 (s, 2H). ^{13}C NMR (CDCl_3) δ 14.0, 23.3, 25.5, 36.6, 54.7, 68.2.

[806] 2-Amino-2-butylhexyl hydrogen sulfate



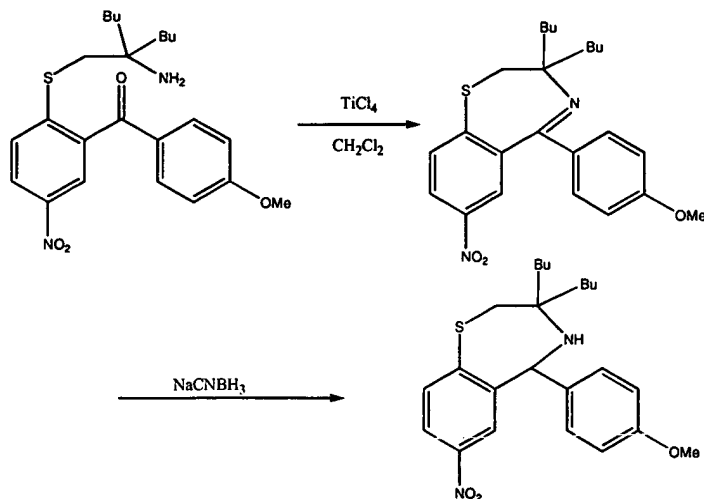
[807] The product of 2-amino-2-butylhexanol (12g) was dissolved in CH_2Cl_2 (120 ml) and treated with chlorosulfonic acid (13.39 g). The reaction mixture was stirred at room temperature overnight. After removing the solvent, the resulting slurry was diluted with acetone, filtered and washed with another 5 ml acetone. The white solid was dried to give 8.1 g product. (yield 46.16%). ^1H NMR (D_2O) δ 0.80 (t, J = 6.6 Hz, 6H), 1.23 (m, 8 H), 1.60 (m, 4H), 3.99 (s, 2H). LC/MS (ES/M + H): 154.1.

[808] 2-(2-Amino-2-butylhexylthio)-4-nitro-(4'-methoxy)-benzophenone



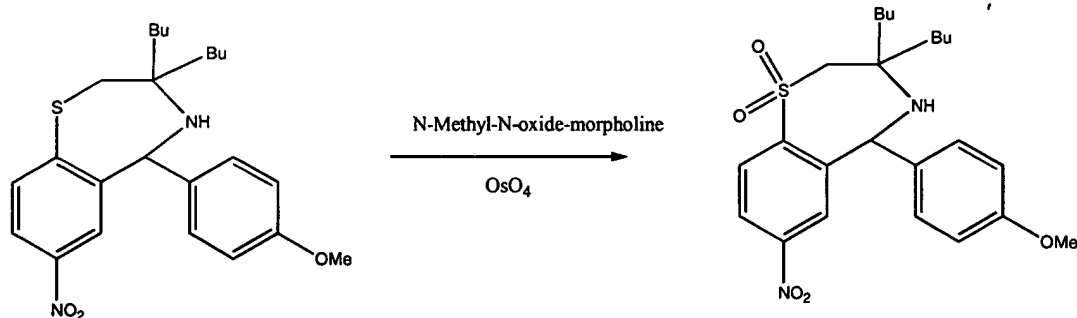
- [809] To a three necked flask was added 2-chloro-4-nitro-(4'-methoxy)-benzophenone (4 g) and 40ml of dimethylacetamide. The reaction mixture was heated to 40°C until the mixture become homogeneous. Sodium sulfide hydrate ($\text{Na}_2\text{S} \cdot 3\text{H}_2\text{O}$) (1.88g, 1.05 eq.) and water (2 ml) were combined in a separated flask and heated to 55°C until homogenous. The Na_2S solution was then added portionwise to the reaction mixture over 20 minutes. After stirred 4 hours at 40°C, the reaction mixture was cooled to 30°C. 2-Amino-2-butylhexyl hydrogen sulfate (3.81g, 1.1 eq.), BuOAc (40 ml) and water (20 ml) was added. The reaction mixture was stirred and heated to an internal temperature of 93 °C and NaOH (1.42 g in 20 ml water) was added dropwise. After complete addition, the reaction was stirred an additional 1 hour at 93 °C, then cooled to room temperature. After separation, the aqueous layer was extracted with EtOAc (2 x 50 ml). Combined organic layers were dried and concentrated in vacuo to give a yellow oil. Flash chromatography on silica gel, eluting with hexane : EtOAc (4:1-1:4), afforded the desired product (near 1.99g) as a yellow oil. (~31%). ^1H NMR (CDCl_3) δ 0.86 (t, J = 6.44 Hz, 6H), 1.12-1.60 (m, 8H), 1.31-1.46 (m, 4H), 3.02 (s, 2H), 3.87 (s, 3H), 6.96 (d, J = 8.86 Hz, 2H), 7.62 (d, J = 8.86 Hz, 1H), 7.77 (d, J = 8.86 Hz, 2H), 8.14 (d, J = 2.42 Hz, 1H), 8.23 (dd, J = 8.86, 2.42 Hz, 1H). ^{13}C NMR (CDCl_3) δ 14.2, 23.4, 26.0, 39.6, 45.8, 54.6, 55.8, 114.4, 123.6, 124.8, 128.4, 129.2, 132.8, 139.7, 144.7, 147.6, 164.6, 193.2. LC/MS (ES/M + H): 445.2.

[810] 3,3-Dibutyl-2,3,4,5-tetrahydro-7-nitro-5-(4'-methoxyphenyl)-1,4-benzothiazepine



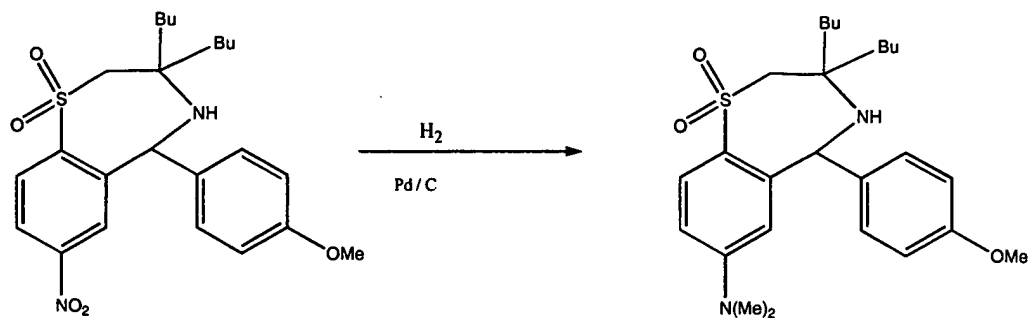
[811] To a three necked flask was added 2-(2-amino-2-butylhexylthio)-4-nitro-(4'-methoxy)-benzophenone (1g), triethyl amine (0.75 ml) and CH_2Cl_2 (40 ml). After the reaction mixture was stirred 20 minutes in an ice-water bath, TiCl_4 (2.25 ml of 1 M solution in CH_2Cl_2) was added via syringe. After stirring overnight, the reaction mixture was carefully quenched with a methanolic solution of NaCNBH_3 (0.84 g) and stirred for 1 hour. The reaction was basified to pH 13 with 5N aq. NaOH, extracted with EtOAc (2 x 100ml) dried and evaporated to a yellow oil. Flash chromatography on silica gel, eluting with EtOAc/hexanes, provide the desired product as a yellow oil. (yield 79.67%). ^1H NMR (CDCl_3) δ 0.82-0.94 (m, 6H), 1.03-1.62 (m, 11H), 1.86-1.99 (m, 1H), 2.77 (d, $J = 14.6\text{Hz}$, 1H), 3.05 (d, $J = 14.6\text{ Hz}$, 1H), 3.86 (s, 3H), 5.50 (s, 1H), 6.95 (d, $J = 8.66\text{ Hz}$, 2H), 7.25 (d, $J = 8.66\text{ Hz}$, 2H), 7.45 (d, $J = 1.81\text{ Hz}$, 1H), 7.62 (d, $J = 8.46\text{ Hz}$, 1H), 7.88 (1H, dd, $J = 8.46, 2.42\text{ Hz}$). LC/MS (ES/M + H): 429.2.

[812] 3,3-Dibutyl-2,3,4,5-tetrahydro-7-nitro-5-(4'-methoxyphenyl)-1,4-benzothiazepine 1,1-dioxide



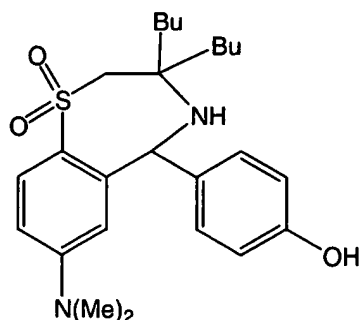
- [813] To a solution of 3,3-dibutyl-2,3,4,5-tetrahydro-7-nitro-5-(4'-methoxyphenyl)-1,4-benzothiazepine (0.91 g) in 20 ml THF and 9 ml tBuOH was added N-methyl-morpholine-N-oxide (0.74g, 3 eq.) and OsO₄ (0.5 ml, 2.5% wt in t-butanol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was transferred to a separatory funnel and partitioned between 100 ml of brine and 100ml of EtOAc. The aqueous layer was extracted three times with EtOAc (3 x 25 ml). The organic layer was dried, concentrated in vacuo. The residue was purified via flash chromatography on silica gel, eluting with 20% EtOAc / hexane to give the desired product (0.82 g). (yield 83.84%). Reverse-phase HPLC: rt = 18.8 min, 99.7% pure. ¹H NMR (CDCl₃) δ 0.90-0.97 (m, 6H), 1.03-1.38 (m, 8H), 1.42-1.50 (m, 2H), 1.57 (br s, 1H), 1.74-1.88 (m, 1H), 2.14-2.26 (m, 1H), 3.32 (q_{AB}, J_{AB} = 15.3 Hz, Δv = 91.7 Hz, 2H), 3.87 (s, 3H), 5.97 (s, 1H), 6.98 (d, J = 8.66 Hz, 2H), 7.30 (d, J = 8.66 Hz, 2H), 7.62 (d, J = 2.02 Hz, 1H), 8.18 (dd, J = 8.46, 2.21 Hz, 1H), 8.30 (d, J = 8.46 Hz, 1H). ¹³C NMR (CDCl₃) δ 13.9, 14.0, 22.8, 23.0, 25.2, 31.7, 40.7, 55.3, 57.2, 63.7, 114.5, 121.8, 123.2, 128.7, 129.2, 132.6, 145.5, 148.3, 150.2, 159.3. HRMS (ES/M + H) calcd for C₂₄H₃₂N₂O₅S: 461.2102, found: 461.2105. Anal Calcd for (C₂₄H₃₂NO₅S): C, 62.58; H, 7.00; N, 6.08; S, 6.96. Found: C, 62.60; H, 7.10; N, 6.01; S, 6.83.

- [814] Example 2; 3,3-Dibutyl-2,3,4,5-tetrahydro-7-dimethylamino-5-(4'-methoxyphenyl)-1,4-benzothiazepine 1,1-dioxide



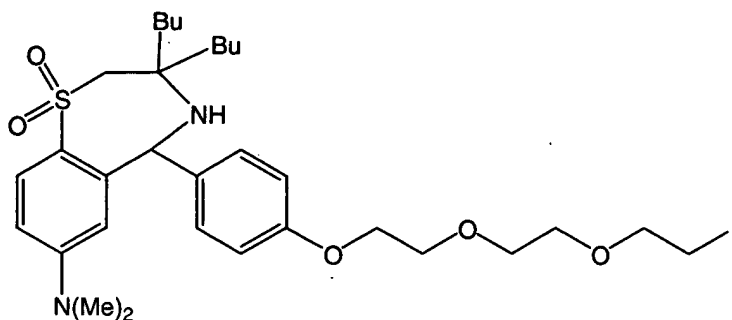
- [815]** 3,3-Dibutyl-2,3,4,5-tetrahydro-7-nitro-5-(4'-methoxyphenyl)-1,4-benzothiazepine 1,1-dioxide (0.768 g), MeOH (60 ml), 10% Pd/C (0.100 g) and formaldehyde (3.14 g/37% in water) were combined in a Fischer Porter bottle. Sulfuric acid (0.020 g) was added to the reaction mixture. The reactor was purged with H₂ and pressurized to 45 psig H₂. After stirring at 50 °C overnight, sodium carbonate (0.2 g) was added and the mixture stirred for 1 hour more. The reaction mixture was filtered through celite and washed with additional MeOH (20 ml). After concentrated, the residue was dissolved in EtOAc (200 ml) and washed with water (100ml) and brine (100 ml). The organic layer was dried and concentrated in vacuo, and the resulting yellow oil was purified by flash chromatography on silica gel, eluting with EtOAc: hexane: triethylamine 20: 80:1, to give 0.43g of product. (Yield 56.23%). Reverse-phase HPLC: rt = 5.9 min, 100% pure. ¹H NMR (CDCl₃) δ 0.81 (t, J = 7.4 Hz, 3H), 0.86 (t, J = 6.9 Hz, 3H), 1.08-1.53 (m, 10H), 1.81 (m, 1H), 2.20 (m, 1H), 2.79 (s, 6H), 3.18 (q_{AB}, J_{AB} = 6.9 Hz, Δv = 116.8 Hz, 2H), 3.83 (s, 3H), 5.92 (s, 1H), 5.96 (s, 1H), 6.46 (d, J = 9.6 Hz, 1H), 6.90 (d, J = 9.6 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.87 (d, J = 9.6 Hz, 1H). Anal Calcd for (C₂₆H₃₈N₂O₃S): C, 68.09; H, 8.35; N, 6.11; S, 6.99; O, 10.46. Found: C, 66.92; H, 8.17; N, 5.99; S, 6.75; O, 10.29.

- [816] 3,3-Dibutyl-2,3,4,5-tetrahydro-7-dimethylamino-5-(4'-hydroxyphenyl)-1,4-benzothiazepine 1,1-dioxide



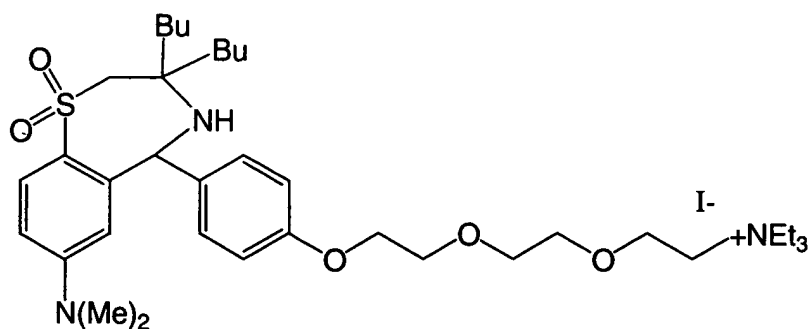
- [817] 3,3-Dibutyl-2,3,4,5-tetrahydro-7-dimethylamino-5-(4'-methoxyphenyl)-1,4-benzothiazepine 1,1-dioxide (0.300 g, 0.655 mmol) was dissolved in CH₂Cl₂ (10 ml). The mixture was cooled to 0 °C, and a solution of 1 M BBr₃ in CH₂Cl₂ (1.96 ml, 1.96 mmol) was added. After 15 min, the cooling bath was removed. After 3 hrs more, the reaction mixture was again cooled to 0 °C and quenched with 10% aq. HCl (9 ml). NaHCO₃ (about 1.0 g) was added until pH = 7, and the mixture was extracted with CH₂Cl₂ (3 x 5 ml). The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with 30% EtOAc/hexane, gave the desired product (0.250 g/86%). Reverse-phase HPLC: rt = 13.6 min, 98.8% pure. ¹H NMR (CDCl₃) δ 0.81 (t, J = 6.9 Hz, 3H), 0.86 (t, J = 6.9 Hz, 3H), 1.05-1.46 (m, 10 H), 1.80 (m, 1H), 2.23 (m, 1H), 2.80 (s, 6H), 3.18 (q_{AB}, J_{AB} = 14.1 Hz, Δν = 119.2 Hz, 2H), 4.79 (s, 1H), 5.92 (s, 1H), 5.96 (s, 1H), 6.47 (d, J = 9.9 Hz, 1H), 6.84 (d, J = 8.1 Hz, 2H), 7.49 (d, J = 9.0 Hz, 2H), 7.88 (d, J = 9.0 Hz, 1H). LC/MS (ES/M + H): 445.. Anal Calcd for (C₂₅H₃₆N₂O₃S): C, 67.53; H, 8.17; N, 6.30; S, 7.20; O, 10.80. Found: C, 67.52; H, 8.20; N, 6.23; S, 7.18; O, 11.00.

- [818] 2-[2-[2-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1,1-dioxido-1,4-benzothiazepin-5-yl]phenoxy]ethoxy]ethoxy]ethoxy iodide



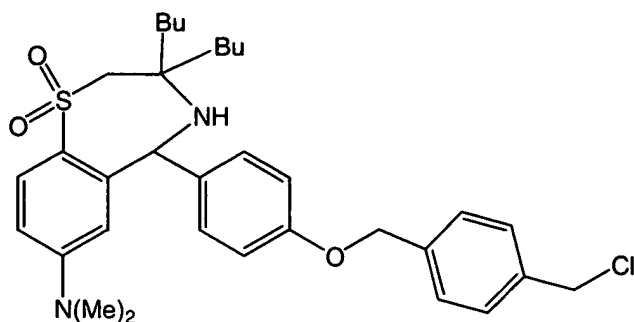
[819] 60% Sodium hydride in mineral oil (0.0100 g, 0.247 mmol) and DMF (1.0 ml) were combined in a 100 ml round-bottom flask. The mixture was cooled to 0 °C, and a solution of 3,3-dibutyl-2,3,4,5-tetrahydro-7-dimethylamino-5-(4'-hydroxyphenyl)-1,4-benzothiazepine 1,1-dioxide (0.100 g, 0.225 mmol) in DMF (1.5 ml) was added. After 1 hr, 1,2-bis-(2-iodoethoxy)ethane (0.832 g, 2.249 mmol) in DMF (1.0 ml) was added. The reaction mixture was allowed to warm to room temperature and was then heated to 40 °C. After 5 hrs, the reaction mixture was diluted with ethyl ether and water. The organic layer was washed with water and brine, dried (Na₂SO₄) and concentrated in vacuo. Purification by circular chromatotron on silica gel, eluting with EtOAc/hexanes gave the desired product (0.075 g/50%). Reverse-phase HPLC: rt = 15.3 min, 96% pure. ¹H NMR (CDCl₃) δ 0.81 (t, J = 7.2 Hz, 3H), 0.86 (t, J = 6.9 Hz, 3H), 1.08-1.55 (m, 10 H), 1.80 (m, 1H), 2.20 (m, 1H), 2.79 (s, 6H), 3.17 (q_{AB}, J_{AB} = 14.1 Hz, Δν = 113.1 Hz, 2H), 3.25 (t, J = 6.9 Hz, 2H), 3.72 (m, 6H), 3.88 (t, J = 4.8 Hz, 2H), 4.14 (t, J = 4.8 Hz, 2H), 5.91 (s, 1H), 5.97 (s, 1H), 6.45 (d, J = 9.0 Hz, 1H), 6.90 (d, J = 7.8 Hz, 2H), 7.31 (d, J = 7.8 Hz, 2H), 7.86 (d, J = 8.7 Hz, 1H). LC/MS (ES/M + H): 687.

[820] Example 4: N-[2-[2-[2-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1,1-dioxido-1,4-benzothiazepin-5-yl]phenoxy]ethoxy]ethoxy]ethoxy]-N,N,N-triethylaminium iodide



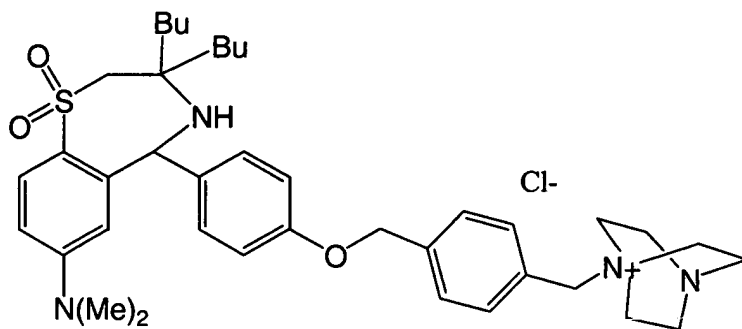
[821] 2-[2-[2-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1,1-dioxido-1,4-benzothiazepin-5-yl]phenoxy]ethoxy]ethoxy]ethoxy iodide (0.0500 g, 0.0729 mmol), Et₃N (0.50 ml, 3.59 mmol) and CH₃CN (0.80 ml) were combined in a 25 ml round-bottom flask. The mixture was heated 40 °C. After 3 days, the mixture was concentrated in vacuo, and the resulting residue was washed repeatedly with ethyl ether to yield the desired product (0.040 g/70%). Reverse-phase HPLC: *rt* = 10.9 min, 97% pure. ¹H NMR (CDCl₃) δ 0.80 (t, *J* = 6.9 Hz, 3H), 0.86 (t, *J* = 6.3 Hz, 3H), 1.11-1.43 (m, 10 H), 1.34 (t, *J* = 6.9 Hz, 9H), 1.78 (m, 1H), 2.15 (m, 1H), 2.80 (s, 6H), 3.24 (q_{AB}, *J*_{AB} = 13.8 Hz, Δ*v* = 155.4 Hz, 2H), 3.50 (q, *J* = 7.2 Hz, 6H), 3.71 (br s, 6H), 3.83 (m, 2H), 4.00 (br s, 2H), 4.11 (m, 2H), 5.92 (s, 1H), 5.96 (s, 1H), 6.47 (d, *J* = 9.6 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.33 (d, *J* = 8.7 Hz, 2H), 7.86 (d, *J* = 8.4 Hz, 1H). LC/MS (ES/M - HI): 659.5..

- [822] 4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1,1-dioxido-1,4-benzothiazepin-5-yl]phenoxy]methyl]phenylmethyl chloride



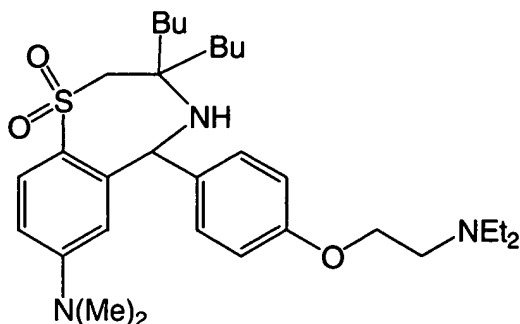
- [823] 3,3-Dibutyl-2,3,4,5-tetrahydro-7-dimethylamino-5-(4'-hydroxyphenyl)-1,4-benzothiazepine 1,1-dioxide (0.070 g, 0.157 mmol), K₂CO₃ (0.033 g, 0.236 mmol) and α,α' -dichloro-p-xylene (0.2756 g, 1.574 mmol) were combined with acetone (2.50 ml). The mixture was heated to 70 °C. After 48 hrs, the mixture was cooled to room temperature and concentrated in vacuo. The residue was dissolved in EtOAc and washed with water. The water washes were extracted with EtOAc. Combined organic layers were washed with brine, dried (Na₂SO₄) and concentrated in vacuo. Purification by circular chromatotron on silica gel, eluting with 20% EtOAc/hexanes, gave the desired product (0.067 g/73%). Reverse-phase HPLC: rt = 19.6 min, 97% pure. ¹H NMR (CDCl₃) δ 0.81 (t, J = 6.9 Hz, 3H), 0.87 (t, J = 6.9 Hz, 3H), 1.12-1.50 (m, 10H), 1.83 (m, 1H), 2.20 (m, 1H), 2.79 (s, 6H), 3.18 (q_{AB}, J_{AB} = 12.6 Hz, $\Delta\nu$ = 116.3 Hz, 2H), 4.59 (s, 2H), 5.08 (s, 2H), 5.91 (s, 1H), 6.00 (s, 1H), 6.48 (d, J = 8.1 Hz, 1H), 6.96 (d, J = 8.1 Hz, 2H), 7.32-7.44 (m, 6H), 7.88 (d, J = 9.3 Hz, 1H). LC/MS (ES/M + H): 583. Anal Calcd for (C₃₃H₄₃N₂O₃SCl): C, 68.01; H, 7.44; N, 4.81; S, 5.49; O, 8.24. Found: C, 67.70; H, 7.21; N, 4.77; S, 5.35; O, 7.98.

[824] Example 5; 1-[[4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1,1-dioxido-1,4-benzothiazepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride



[825] A solution of 4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1,1-dioxido-1,4-benzothiazepin-5-yl]phenoxy]methyl]phenylmethyl chloride (0.045 g, 0.0773 mmol), in CH₃CN (1.50 ml) was added dropwise to a solution of 1,4-diazabicyclo[2.2.2]octane (0.086 g, 0.773 mmol) in CH₃CN (1.00 ml) over a period of 30 min. at 40 °C. After 2 hrs, the reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was washed repeatedly with ethyl ether and concentrated in vacuo to give the desired product (0.045 g/83%). Reverse-phase HPLC: *rt* = 13.0 min, 97% pure. ¹H NMR (CDCl₃) δ 0.80 (t, *J* = 6.9 Hz, 3H), 0.87 (t, *J* = 6.9 Hz, 3H), 1.10-1.48 (m, 10), 1.76 (m, 1H), 2.17 (m, 1H), 2.81 (s, 6H), 3.18 (br s, 6H), 3.19 (q_{AB}, *J*_{AB} = 14.7 Hz, Δ*v* = 113.0 Hz, 2H), 3.75 (br s, 6H), 5.08 (s, 2H), 5.12 (s, 2H), 5.92 (s, 1H), 5.99 (s, 1H), 6.47 (d, *J* = 8.7 Hz, 1H), 6.95 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 9.6 Hz, 2H), 7.51 (d, *J* = 7.5 Hz, 2H), 7.65 (d, *J* = 7.8 Hz, 2H), 7.86 (d, *J* = 8.1 Hz, 1H). LC/MS (ES/M - HCl): 659. Anal Calcd for (C₃₉H₅₅N₄O₃SCl₃·3H₂O): C, 62.50; H, 8.20; N, 7.48; S, 4.28; O, 12.81. Found: C, 62.30; H, 7.82; N, 7.43; S, 4.20; O, 12.86.

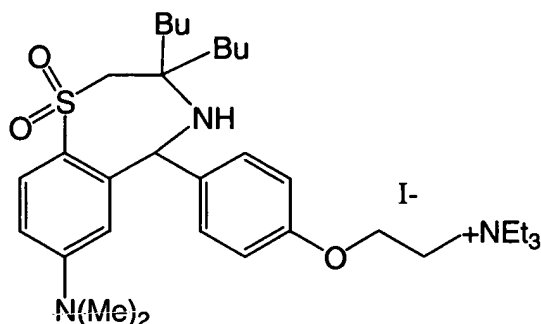
[826] N-[2-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1,1-dioxido-1,4-benzothiazepin-5-yl]phenoxy]ethyl]-N,N-diethylamine



[827] In a 250 ml round-bottom flask, NaOH (3.5 ml, 3.5 mmol, 1N in water) was added to a mixture of 2-diethylamino ethyl chloride (0.4257 g, 2.474 mmol) in ethyl ether (3.5 ml) at 0 °C. The mixture was allowed to warm to room temperature and was extracted with ethyl ether. The organic layer was dried (K₂CO₃) for 2 hrs.

[828] In a separate 100 ml round-bottom flask, NaH (0.020 g, 0.50 mmol, 60% in mineral oil) was suspended in DMF (1.0 ml). The mixture was cooled to 0 °C and a solution of PHA-404434 3,3-dibutyl-2,3,4,5-tetrahydro-7-dimethylamino-5-(4'-hydroxyphenyl)-1,4-benzothiazepine 1,1-dioxide (0.110 g, 0.2474 mmol) in DMF (1.5 ml) was added. After 0.5 hrs, the diethylamino ethyl chloride solution was added. The resulting mixture was heated to 40 °C overnight. The reaction mixture was then cooled to room temperature and diluted with ethyl ether. The mixture was washed with 5% aq. NaOH (3 ml), water (10 ml) and brine (10 ml). The organic layer was dried (Na₂SO₄) and concentrated in vacuo. Purification by reverse-phase HPLC, eluting with 5-100% CH₃CN/H₂O, gave the desired product (0.064 g/48%). Reverse-phase HPLC: rt = 11.6 min, 99% pure. ¹H NMR (CDCl₃) δ 0.80 (t, J = 6.9 Hz, 3H), 0.86 (t, J = 6.6 Hz, 3H), 1.05 (t, J = 6.9 Hz, 6H), 1.12-1.41 (m, 10H), 1.79 (m, 1H), 2.21 (m, 1H), 2.63 (q, J = 7.2 Hz, 4H), 2.78 (s, 6H), 2.88 (t, J = 6.0 Hz, 2H), 3.16 (q_{AB}, J_{AB} = 14.4 Hz, Δv = 116.1 Hz, 2H), 4.06 (t, J = 6.3 Hz, 2H), 5.92 (s, 1H), 5.96 (s, 1H), 6.46 (d, J = 8.7 Hz, 1H), 6.90 (d, J = 9.0 Hz, 2H), 7.30 (d, J = 9.0 Hz, 2H), 7.87 (d, J = 8.7 Hz, 1H). LC/MS (ES/M + H): 544.

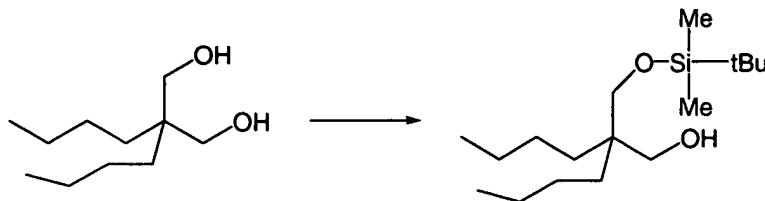
[829] Example 3; N-[2-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1,1-dioxido-1,4-benzothiazepin-5-yl]phenoxy]ethyl]-N,N,N-triethylaminium iodide



[830] N-[2-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1,1-dioxido-1,4-benzothiazepin-5-yl]phenoxy]ethyl]-N,N-diethylamine (0.030 g, 0.0552 mmol), ethyl iodide (0.005 ml, 0.0619 mmol) and CH₃CN (0.50 ml) were combined in a 10 ml vial and heated to 40 °C. After 18 hrs, additional ethyl iodide (0.010 ml, 0.124 mmol) was added. After 24 hrs more, additional ethyl iodide (0.010 ml, 0.124 mmol) was added. After 18 hrs more, the mixture was concentrated in vacuo, and the residue was washed with ethyl ether to give the desired product (0.032 g/100%). Reverse-phase HPLC: rt = 12.3 min, 97% pure. ¹H NMR (CDCl₃) δ 0.80 (t, J = 7.2 Hz, 3H), 0.86 (t, J = 7.2 Hz, 3H), 1.08-1.40 (m, 10H), 1.49 (t, J = 7.2 Hz, 9H), 1.78 (m, 1H), 2.15 (m, 1H), 2.82 (s, 6H), 3.17 (q_{AB}, J_{AB} = 13.8 Hz, Δv = 125.2 Hz, 2H), 3.60 (q, J = 7.2 Hz, 6H), 4.10 (d, J = 4.8 Hz, 2H), 4.53 (s, 2H), 5.88 (s, 1H), 6.10 (s, 1H), 6.47 (d, J = 8.1 Hz, 1H), 6.92 (d, J = 7.8 Hz, 2H), 7.38 (d, J = 7.8 Hz, 2H), 7.87 (d, J = 7.8 Hz, 1H). LC/MS (ES/M + H): 583.

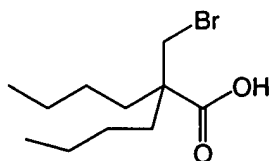
[831] Synthesis of 1,5 benzothiazepines Scheme IV

[832] 1-dimethyl,t-butylsilyl, 2,2-dibutyl-1,3-propanediol



[833] A solution of 2,2-dibutyl-1,3-propanediol (18.8 g, 100 mmol) in THF (60 ml) was added to a slurry of NaH (4.00 g, 100 mmol, 40% in mineral oil) in THF (100 ml). After 1 hr, the mixture was cooled to 0 °C, and tBuMe₂SiCl (100 ml, 100 mmol, 1M in THF) was added. The mixture was allowed to warm to room temp. overnight. The mixture was concentrated in vacuo, and the residue was treated with water (750 ml) and ethyl ether (60 ml). The ether layer was washed with aq. NaHCO₃ and brine, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with 5% EtOAc/hexane, gave the desired product (27.3 g/90%). ¹H NMR (CDCl₃) δ 0.05 (s, 6H), 0.86 (s, 6H), 0.88 (s, 9H), 1.20 (m, 12H), 3.50 (s, 4H). ¹³C NMR (CDCl₃) δ -5.7, 14.0, 18.1, 23.6, 25.1, 25.8, 30.6, 40.8, 69.6, 70.2. GC/MS (ES/M - tBu): 245. Anal Calcd for (C₁₇H₃₈O₂Si): C, 67.48; H, 12.66. Found: C, 67.98; H, 12.81.

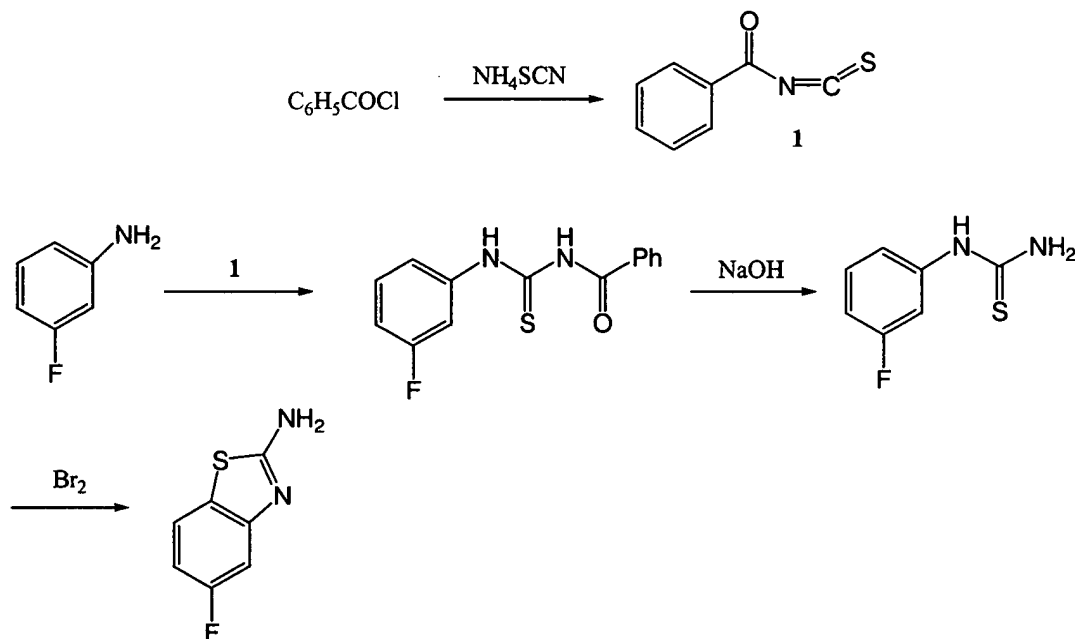
[834] 2-bromomethyl-2-butyl hexanoic acid



[835] Sodium periodate (17.67 g, 82.62 mmol) and RuCl₃ (0.125 g, 0.603 mmol) were added to a solution of 2-[[t-butyl(dimethylsilyl)oxy]methyl]-2-butylhexanol (10.0 g, 33.05 mmol) in CCl₄ (20.0 ml), CH₃CN (20.0 ml) and water (30.0 ml) at 0 °C. After stirring for 20 hrs at room temp, the mixture was filtered through celite, extracted with CH₂Cl₂ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel, eluting with 20% EtOAc/hexane. The resulting residue

was taken up in 48% HBr (35 ml) and heated to reflux. After 24 hrs, the mixture was cooled to room temp, and extracted with ethyl ether (3x). The combined extracts were washed with brine, dried (Na₂SO₄) and concentrated in vacuo. Purification by sublimation at 50 °C under vacuum gave a white solid (5.26 g/60%). ¹H NMR (CDCl₃) δ 0.89 (t, J = 7.0 Hz, 6H), 1.11-1.24 (m, 4H), 1.25-1.34 (m, 4H), 1.65-1.69 (m, 4H), 3.56 (s, 2H). ¹³C NMR (CDCl₃) δ 13.9, 22.9, 26.0, 34.1, 36.2, 50.2, 180.9. MS (ES/M - HBr -H): 182.6. Anal Calcd for (C₁₁H₂₁O₂Br): C, 49.82; H, 7.98; Br, 30.13. Found: C, 49.94; H, 7.96; Br, 30.30.

[836] 2-Amino-5-fluorobenzothiazole

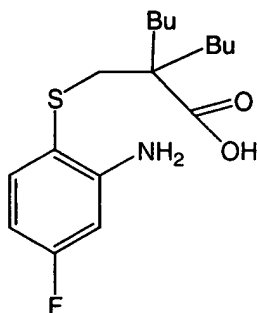


[837] Benzoyl chloride (34.72 g, 247 mmol) was added to a mixture of ammonium thiocyanate (18.8 g, 247 mmol) and acetone (100.0 ml) at 30 °C. The mixture was heated to reflux for 10 min, and then 3-fluoroaniline (25.0 g, 225 mmol) was added at 50 °C over 10 min. Additional acetone (20 ml) was added, and the mixture was heated to reflux for 1 hr. A solution of NaOH (28.76 g, 719 mmol) in water (166 ml) was added, and the resulting solution was heated to reflux. After 1.5 hrs, the mixture

was cooled to room temperature and concentrated to remove the acetone. Concentrated aq. HCl was added until pH = 5.0. Then, concentrated aq. NH₄OH was added until pH = 11.0. The precipitate was filtered, washed with water and dried via vacuum oven to give 3-fluorophenylthiourea (32 g/84%).

- [838] A solution of bromine (29.08 g, 182 mmol) in CH₂Cl₂ (80 ml) was added to a solution of 3-fluorophenylthiourea (31.0 g, 182 mmol) in CH₂Cl₂ (550 ml). The mixture was heated to reflux. After 3 hrs, the reaction mixture was cooled to room temp and filtered. The solid was suspended in water (1 L) and conc. NH₄OH was added until basic. The mixture was extracted with EtOAc (3 x 200 ml). Combined organic extracts were washed with water (150 ml) and brine (150 ml), dried (Na₂SO₄) and concentrated in vacuo to give a colored solid. Recrystallization from benzene gave the desired product as a white solid (18.9 g/50%). ¹H NMR (DMSO-d₆) δ 6.83 (t, J = 7.7 Hz, 1H), 7.10 (d, J = 10.5 Hz, 1H), 7.59-7.64 (m, 3H). LC/MS (ES/M + H): 168.9. Anal Calcd for (C₇H₅N₂SF): C, 49.99; H, 3.00; N, 16.66; S, 19.06. Found: C, 50.04; H, 2.95; N, 16.57; S, 18.96.

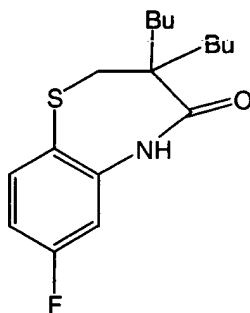
- [839] 2-(((2-amino-4-fluorophenyl)thio)methyl)-2-butylhexanoic acid



- [840] Potassium hydroxide (1.76 g, 31.52 mmol) was added to a suspension of 2-amino-5-fluorobenzothiazole (0.278 g, 1.65 mmol) in water (3.5 ml). The mixture was heated to reflux for 7 hrs and then allowed to cool to room temp. 2-(Bromomethyl)-2-butylhexanoic acid (0.44 g, 1.65 mmol) was added. After 18 hrs more, conc. aq. HCl was added until pH = 4. The mixture was extracted with EtOAc, dried (Na₂SO₄), and concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with 10-40% EtOAc/hexane, gave the desired product (0.459 g/85%). ¹H NMR

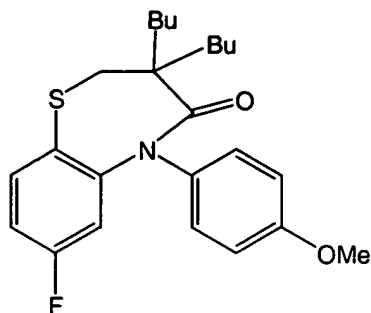
(CD₃OD) δ 0.81 (t, J = 7.0 Hz, 6H), 1.00-1.13 (m, 4H), 1.15-1.22 (m, 4H), 1.50-1.68 (m, 4H), 2.92 (s, 2H), 6.24 (dt, J = 8.5, 2.6 Hz, 1H), 6.41 (dd, J = 11.1, 2.8 Hz, 1H), 7.26 (dd, J = 8.5, 6.4 Hz, 1H). LC/MS (ES/M - C₁₁H₂₁O₂): 141.9. Anal Calcd for (C₁₇H₂₆NO₂SiF): C, 62.35; H, 8.01; N, 4.28; S, 9.77. Found: C, 62.23; H, 8.28; N, 4.09; S, 9.06.

[841] 3,3-Dibutyl-2,3-dihydro-5H-7-fluoro-1,5-benzothiazepine-4-one



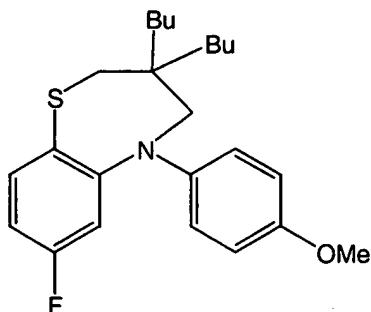
[842] p-Toluenesulfonic acid (0.426 g, 2.24 mmol) was added to a suspension of 2-(((2-amino-4-fluorophenyl)thio)methyl)-2-butylhexanoic acid (9.1 g, 27.8 mmol) in tetradecane (130.0 ml). The mixture was heated to reflux, collecting water in a Dean-Stark trap. After 15 min, the mixture was cooled to room temp and purified by flash chromatography on silica gel, eluting with 0-10% EtOAc/hexane to give the desired product (4.60 g/50%). ¹H NMR (CDCl₃) δ 0.85 (t, J = 6.8 Hz, 6H), 1.24 (m, 8H), 1.60 (m, 2H), 1.80 (m, 2H), 2.90 (s, 2H), 6.68-6.74 (m, 2H), 7.38 (dd, J = 9.1, 6.4 Hz, 1H), 7.94 (s, 1H). Anal Calcd for (C₁₇H₂₄NOSF): C, 65.99; H, 7.82; N, 4.53; S, 10.34. Found: C, 66.05; H, 7.91; N, 4.56; S, 10.25.

[843] 3,3-Dibutyl-2,3-dihydro-7-fluoro-5-(4'-methoxyphenyl)-1,5-benzothiazepine-4-one



- [844] A mixture of 2,3-dihydro-3,3-dibutyl-5H-7-fluoro-1,5-benzothiazepine-4-one (4.7 g, 15.2 mmol), 4-iodoanisole (3.91 g, 16.7 mmol), K_2CO_3 (4.19 g, 30.4 mmol), CuI (0.284 g, 1.52 mmol), tris(3,6-dioxaheptyl)amine (0.182 g, 0.56 mmol) and xylenes (40 ml) were heated to reflux, collecting any water present with a Dean-Stark trap. After 48 hrs, the mixture was cooled to room temp, diluted with $CHCl_3$ and purified by flash chromatography on silica gel, eluting with 0-15% EtOAc/hexane, to give the desired product (6.20 g/90%). 1H NMR ($CDCl_3$) δ 0.83 (t, J = 6.9 Hz, 6H), 1.16-1.25 (m, 8H), 1.51 (m, 4H), 3.07 (s, 2H), 3.76 (s, 3H), 6.58 (dd, J = 9.9, 2.7 Hz, 1H), 6.77-6.88 (m, 3H), 7.04 (d, J = 8.7 Hz, 2H), 7.57 (dd, J = 8.7, 6.6 Hz, 1H). LC/MS (ES/M + H): 416.1. Anal Calcd for ($C_{24}H_{30}NO_2SF$): C, 69.36; H, 7.28; N, 3.37; S, 7.70. Found: C, 69.76; H, 7.51; N, 3.39; S, 7.60.

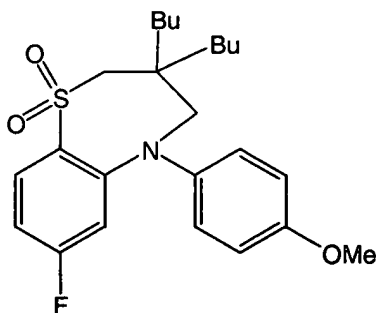
- [845] 3,3-Dibutyl-2,3,4,5-tetrahydro-7-fluoro-5-(4'-methoxyphenyl)-1,5-benzothiazepine



- [846] Sulfuric acid (3.56 ml, 25.7 mmol, 7.2M in THF) was added to a 1M solution of $LiAlH_4$ (51.0 ml, 51.0 mmol) in ethyl ether at 0 °C. After 1 hr, a solution of 3,3-dibutyl-2,3-dihydro-7-fluoro-5-(4'-methoxyphenyl)-1,5-benzothiazepine-4-one (6.20 g, 14.9 mmol) in THF (45.0 ml) was added. The mixture was allowed to warm to room temp. After 3.5 hrs, the mixture was cooled to 0 °C and 30% water/THF (10

ml, v/v) was added. A solution of 1 N aq. NaOH (10.0 ml) was added, and the reaction mixture was filtered through a fritted funnel. The filtrate was extracted with ethyl ether, dried (Na₂SO₄) and concentrated in vacuo to give the desired product (4.68 g/ 78%). ¹H NMR (CDCl₃) δ 0.76 (t, J = 6.6 Hz, 6H), 0.94-1.28 (m, 12H), 2.90 (s, 3H), 3.77 (s, 2H), 3.78 (s, 2H), 6.13 (dd, J = 11.9, 2.6 Hz, 1H), 6.34-6.40 (m, 1H), 6.84 (d, J = 9.1 Hz, 2H), 7.03-7.10 (m, 3H). ¹³C NMR (CDCl₃) δ 13.9, 23.2, 25.3, 33.1, 40.3, 41.8, 55.5, 58.3, 107.1 (d, J = 22.3 Hz), 107.5 (d, J = 25.2 Hz), 114.9, 120.0, 126.3, 131.4 (d, J = 9.2 Hz), 142.0, 151.3 (d, J = 10.0 Hz), 155.9, 161.6 (d, J = 243.0 Hz). Anal Calcd for (C₂₄H₃₂NOSF): C, 71.78; H, 8.04; N, 3.49; S, 7.97. Found: C, 71.70; H, 8.08; N, 3.59; S, 7.89.

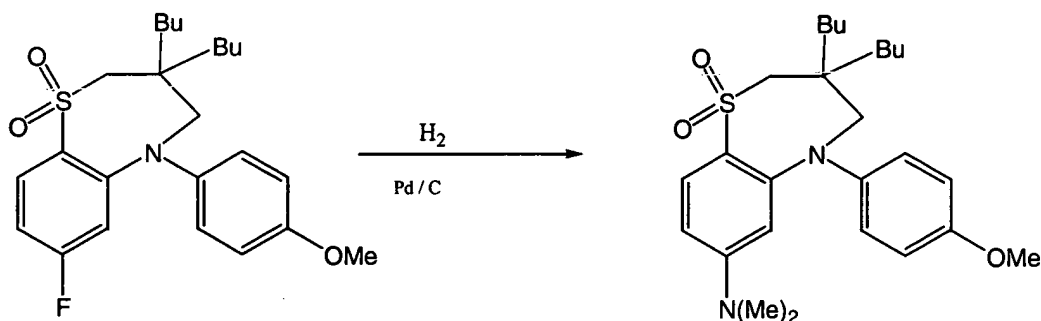
[847] 3,3-Dibutyl-2,3,4,5-tetrahydro-7-fluoro-5-(4'-methoxyphenyl)-1,5-benzothiazepine 1,1-dioxide



[848] A solution of oxone (1.35 g, 2.20 mmol) in water (4.0 ml) was added to a cold (0 °C) solution of 3,3-dibutyl-2,3,4,5-tetrahydro-7-fluoro-5-(4'-methoxyphenyl)-1,5-benzothiazepine (0.40 g, 1.0 mmol) in MeOH (4.0 ml) and THF (15.0 ml). After 16 hrs, the mixture was diluted with water and extracted with CHCl₃ (3x). The combined extracts were washed with water, dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with 25% EtOAc/hexane, gave the desired

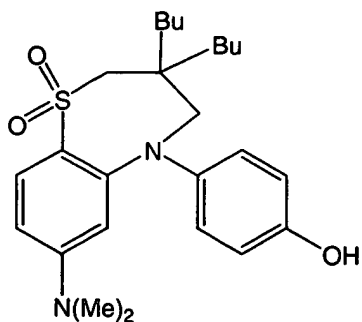
[849] product (0.35 g/80%). ^1H NMR (CDCl_3) δ 0.77 (t, J = 6.4, 6H), 0.86-1.24 (m, 8H), 1.33-1.57 (m, 4H), 3.25 (s, 2H), 3.81 (s, 3H), 3.85 (s, 2H), 6.18 (dd, J = 11.7, 2.4 Hz, 1H), 6.60-6.66 (m, 1H), 6.91 (d, J = 8.9 Hz, 2H), 7.12 (d, J = 9.1 Hz, 2H), 7.94 (dd, J = 9.1, 6.5 Hz, 1H). LC/MS (ES/M + H): 434. Anal Calcd for ($\text{C}_{24}\text{H}_{32}\text{NO}_3\text{SF}$): C, 66.48; H, 7.44; N, 3.23; S, 7.38. Found: C, 66.97; H, 7.63; N, 3.12; S, 7.27.

[850] Example 6; 3,3-Dibutyl-2,3,4,5-tetrahydro-7-dimethylamino-5-(4'-methoxyphenyl)-1,5-benzothiazepine 1,1-dioxide



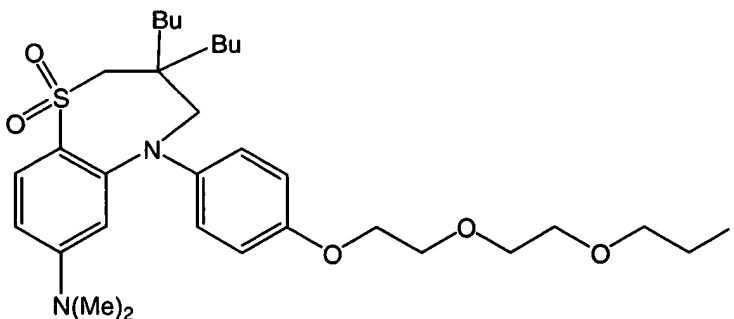
[851] In a Fischer Porter bottle, a solution of 3,3-dibutyl-2,3,4,5-tetrahydro-7-fluoro-5-(4'-methoxyphenyl)-1,5-benzothiazepine 1,1-dioxide (1.00 g, 2.30 mmol) in THF (7.0 ml) was cooled to 0 °C. Dimethylamine (23.0 ml, 46 mmol, 2M in THF) was added, and the vessel was closed and heated to 110 °C. After 16 hrs, the reaction mixture was cooled to room temp and concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with 25% EtOAc/hexane, gave the desired product (0.30 g/28%). ^1H NMR (CDCl_3) δ 0.76 (t, J = 6.8 Hz, 6H), 1.00-1.15 (m, 8H), 1.42-1.51 (m, 4H), 2.79 (s, 6H), 3.15 (s, 2H), 3.71 (s, 2H), 3.79 (s, 3H), 5.81 (d, J = 2.4 Hz, 1H), 6.34 (dd, J = 9.1, 2.4 Hz, 1H), 6.84 (d, J = 8.9 Hz, 2H), 7.11 (d, J = 8.9 Hz, 2H), 7.79 (d, J = 9.1 Hz, 1H). LC/MS (ES/M + H): 459.1. Anal Calcd for ($\text{C}_{26}\text{H}_{38}\text{N}_2\text{O}_3\text{S}$): C, 68.08; H, 8.36; N, 6.11; S, 6.89. Found: C, 68.19; H, 8.28; N, 6.04; S, 6.90.

[852] 3,3-Dibutyl-2,3,4,5-tetrahydro-7-dimethylamino-5-(4'-hydroxyphenyl)-1,5-benzothiazepine 1,1-dioxide



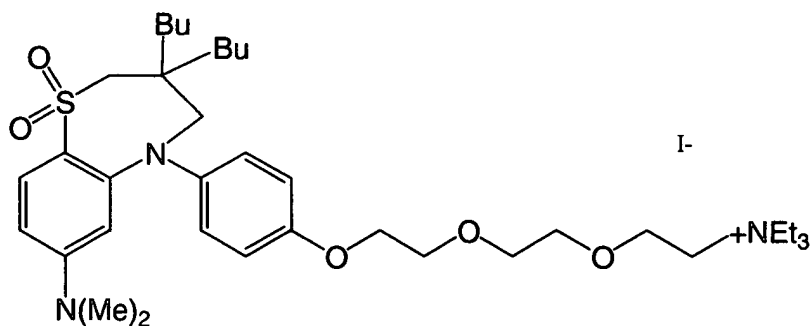
- [853] A solution of 3,3-dibutyl-2,3,4,5-tetrahydro-7-dimethylamino-5-(4'-methoxyphenyl)-1,5-benzothiazepine 1,1-dioxide (0.460 g, 1.003 mmol) in CH_2Cl_2 (6.0 ml) was cooled to 0 °C. Boron tribromide (1.40 ml, 1.49 mmol, 1M in CH_2Cl_2) was added, and the mixture was allowed to warm to room temperature. After 18 hrs, the mixture was cooled to 0 °C, and water (4.0 ml) was added. The mixture was extracted with CH_2Cl_2 (3x). Combined extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography on silica gel, eluting with 30% EtOAc/hexane, gave the desired product (0.30 g/75%). ^1H NMR (CDCl_3) δ 0.78 (t, J = 6.8 Hz, 6H), 1.07-1.16 (m, 8H), 1.43 (m, 4H), 2.80 (s, 6H), 3.17 (s, 2H), 3.70 (s, 2H), 5.12 (s, 1H), 5.81 (d, J = 2.4 Hz, 1H), 6.33 (dd, J = 9.1, 2.6 Hz, 1H), 6.79 (d, J = 8.9 Hz, 2H), 7.06 (d, J = 8.7 Hz, 2H), 7.80 (d, J = 9.1 Hz, 1H). LC/MS (ES/M + H): 445 Anal Calcd for ($\text{C}_{25}\text{H}_{36}\text{N}_2\text{O}_3\text{S}$): C, 67.53; H, 8.17; N, 6.30; S, 7.20. Found: C, 67.37; H, 8.04; N, 6.23; S, 7.15.

- [854] 2-[2-[2-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1,1-dioxido-1,5-benzothiazepin-5-yl]phenoxy]ethoxy]ethoxy]ethoxy iodide



[855] 3,3-Dibutyl-2,3,4,5-tetrahydro-7-dimethylamino-5-(4'-hydroxyphenyl)-1,5-benzothiazepine 1,1-dioxide (0.50 g, 1.12 mmol) was reacted with 1,2-bis(2-iodoethoxy)ethane (4.16 g, 11.24 mmol), according to the procedure described for PHA-426998 above, to give the desired product (0.500 g/71%). ¹H NMR (CDCl₃) δ 0.76 (t, J = 6.6 Hz, 6H), 1.03-1.14 (m, 8H), 1.43 (m, 4H), 2.79 (s, 6H), 3.14 (s, 2H), 3.25 (t, J = 7.0 Hz, 2H), 3.69-3.78 (m, 8H), 3.86 (t, J = 4.8 Hz, 2H), 4.10 (t, J = 4.4 Hz, 2H), 5.79 (d, 2.2 Hz, 1H), 6.33 (dd, J = 8.9, 2.4 Hz, 1H), 6.85 (d, J = 8.9 Hz, 2H), 7.09 (d, J = 8.9 Hz, 2H), 7.78 (d, J = 9.1 Hz, 1H). Reverse-phase HPLC: rt = 28.3 min, 99% pure. LC/MS (ES/M + H): 687.23. Anal Calcd for (C₃₃H₄₇N₃O₅SI): C, 54.21; H, 6.90; N, 4.08; S, 4.66. Found: C, 54.20; H, 6.76; N, 4.03; S, 4.54.

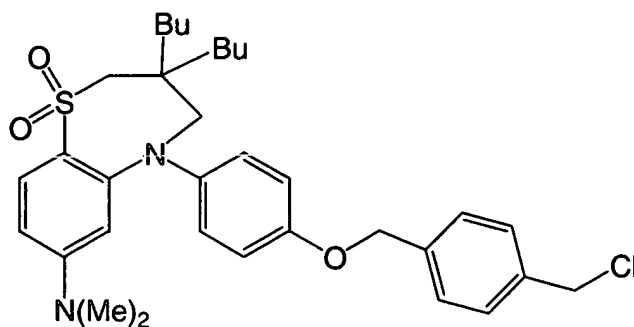
[856] Example 8; N-[2-[2-[2-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1,1-dioxido-1,5-benzothiazepin-5-yl]phenoxy]ethoxy]ethoxy]ethoxy]-N,N,N-triethylaminium iodide



[857] 2-[2-[2-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1,1-dioxido-1,5-benzothiazepin-5-yl]phenoxy]ethoxy]ethoxy]ethoxy iodide (0.34 g, 0.496 mmol) was reacted with Et₃N (1.00 g, 9.88 mmol), according to the procedure described for PHA-426999E above, to give the desired product (0.270 g/69%). ¹H NMR (CDCl₃) δ 0.77 (t, J = 6.6 Hz, 6H), 1.03-1.21 (m, 8H), 1.34 (t, J = 7.2 Hz, 9H), 1.35-1.55 (m, 4H), 2.82 (s, 6H), 3.11 (s, 2H), 3.50 (q, J = 7.2 Hz, 6H), 3.64-3.72 (m, 8H), 3.81 (m, 2H), 4.00 (br s, 2H), 4.08 (m, 2H), 5.89 (d, J = 2.4 Hz, 1H), 6.37 (dd, J = 9.1, 2.4 Hz, 1H), 6.82 (d, J = 8.9 Hz, 2H), 7.06 (d, J = 8.9 Hz, 2H), 7.78 (d, J = 9.1 Hz, 1H). Reverse-phase HPLC: rt = 6.8 min, 98% pure. LC/MS (ES/M - HI): 659.5. Anal

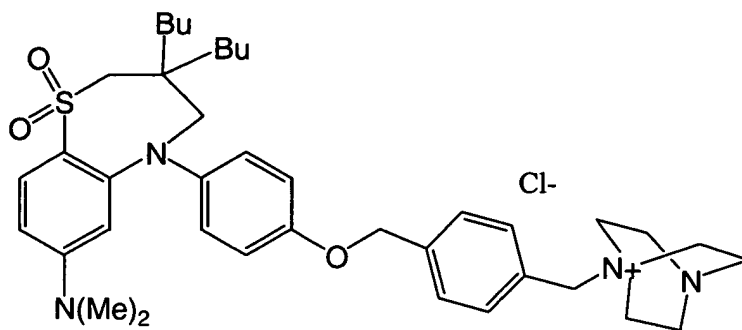
Calcd for (C₃₇H₆₂N₃O₅SI): C, 56.39; H, 7.94; N, 5.34; S, 4.06; O, 10.16; I, 16.12.
 Found: C, 55.01; H, 7.95; N, 5.32; S, 3.96; O, 11.06; I, 16.80.

- [858] 4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1,1-dioxido-1,5-benzothiazepin-5-yl]phenoxy]methyl]phenylmethyl chloride



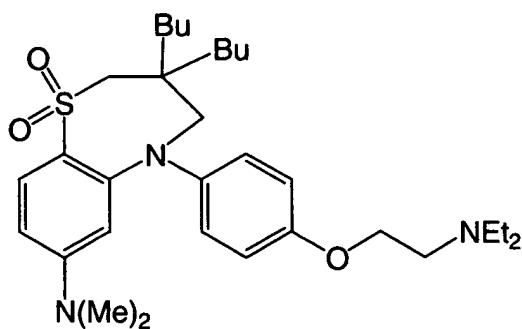
- [859] 3,3-Dibutyl-2,3,4,5-tetrahydro-7-dimethylamino-5-(4'-hydroxyphenyl)-1,5-benzothiazepine 1,1-dioxide (0.50 g, 1.12 mmol) was reacted with α,α' -dichloro-p-xylene (1.968 g, 11.24 mmol), according to the procedure described for PHA-404691 above, to give the desired product (0.300 g/50%). ¹H NMR (CDCl₃) δ 0.76 (t, J = 6.6 Hz, 6H), 0.98-1.14 (m, 8H), 1.43 (m, 4H), 2.79 (s, 6H), 3.14 (s, 2H), 3.69 (s, 2H), 4.58 (s, 2H), 5.04 (s, 2H), 5.81 (d, J = 2.4 Hz, 1H), 6.33 (dd, J = 9.1, 2.4 Hz, 1H), 6.89 (d, J = 8.9 Hz, 2H), 7.10 (d, J = 8.9 Hz, 2H), 7.39 (m, 4H), 7.79 (d, J = 9.1 Hz, 1H). LC/MS (ES/M + 1): 583. HRMS (ES/M + H) calcd for C₃₃H₄₃N₂O₃SCl: 583.2761, found: 583.2773. Anal Calcd for (C₃₃H₄₃N₂O₃SCl): C, 68.01; H, 7.44; N, 4.81; S, 5.49. Found: C, 67.97; H, 7.41; N, 4.83; S, 5.41.

- [860] Example 9 1-[[4-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1,1-dioxido-1,5-benzothiazepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride



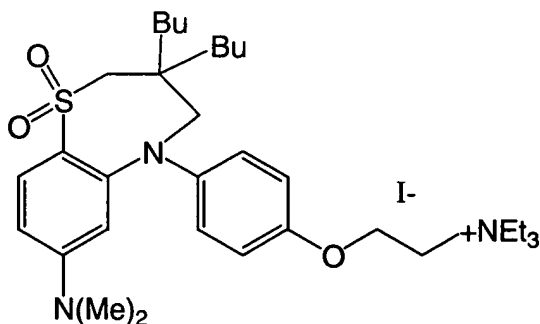
[861] 4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1,1-dioxido-1,5-benzothiazepin-5-yl]phenoxy]methyl]phenylmethyl chloride (0.10 g, 0.17 mmol) was reacted with 1,4-diazabicyclo[2.2.2]octane, according to the procedure described for PHA-409705E, to give desired product (0.100 g/84%). ¹H NMR (CDCl₃) δ 0.76 (t, J = 6.6 Hz, 6H), 1.06-1.21 (m, 8H), 1.42 (m, 4H), 2.82 (s, 6H), 3.12 (s, 2H), 3.14 (t, J = 7.0 Hz, 6H), 3.66 (s, 2H), 3.73 (t, J = 7.0 Hz, 6H), 5.04 (s, 2H), 5.07 (s, 2H), 5.88 (d, J = 2.4 Hz, 1H), 6.36 (dd, J = 11.4, 2.6 Hz, 1H), 6.88 (d, J = 8.9 Hz, 2H), 7.09 (d, J = 9.1 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 9.1 Hz, 1H). Reverse-phase HPLC: rt = 18.1 min, 98.1% pure. LC/MS (ES/M - Cl): 659. HRMS (ES/M - Cl) calcd for C₃₉H₅₅N₄O₃SCl: 659.3995, found: 659.4021. Anal Calcd for (C₃₉H₅₅N₄O₃SCl.3H₂O): C, 62.50; H, 8.20; N, 7.48; S, 4.28; O, 12.81. Found: C, 62.87; H, 7.93; N, 7.40; S, 4.29; O, 11.37.

[862] N-[2-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1,1-dioxido-1,5-benzothiazepin-5-yl]phenoxy]ethyl]-N,N-diethylamine



[863] 3,3-Dibutyl-2,3,4,5-tetrahydro-7-dimethylamino-5-(4'-hydroxyphenyl)-1,5-benzothiazepine 1,1-dioxide (0.50 g, 1.12 mmol) was reacted with 2-diethylamino ethyl chloride (1.935 g, 11.24 mmol), according to the procedure described for the corresponding 1,4-benzothiazepine above, to give the desired product (0.500 g/81%). ¹H NMR (CDCl₃) δ 0.76 (t, J = 6.6 Hz, 6H), 0.97-1.17 (m, 8H), 1.06 (t, J = 7.2 Hz, 6H), 1.43 (m, 4H), 2.63 (dd, J = 14.3, 7.0 Hz, 4H), 2.78 (s, 6H), 2.85 (t, J = 6.0 Hz, 2H), 3.15 (s, 2H), 3.70 (s, 2H), 4.02 (t, J = 6.2 Hz, 2H), 5.78 (d, J = 2.4 Hz, 1H), 6.31 (dd, J = 9.1, 2.4 Hz, 1H), 6.84 (d, J = 8.9 Hz, 2H), 7.09 (d, J = 8.9 Hz, 2H), 7.78 (d, J = 9.1 Hz, 1H). Reverse-phase HPLC: rt = 5.4 min, 99% pure. LC/MS (ES/M + H): 544. Anal Calcd for (C₃₁H₄₉N₃O₃S): C, 68.47; H, 9.08; N, 7.73; S, 5.90; O, 8.83. Found: C, 67.99; H, 8.92; N, 7.79; S, 5.86; O, 9.19.

[864] Example 7; N-[2-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1,1-dioxido-1,5-benzothiazepin-5-yl]phenoxy]ethyl]-N,N,N-triethylammonium iodide

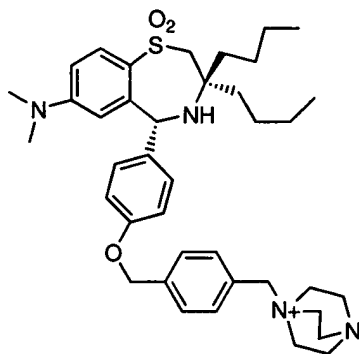
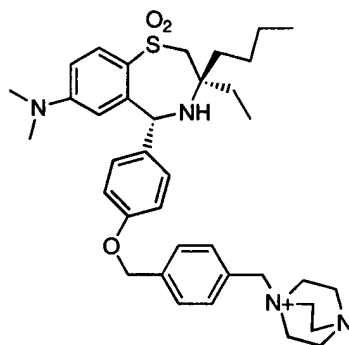
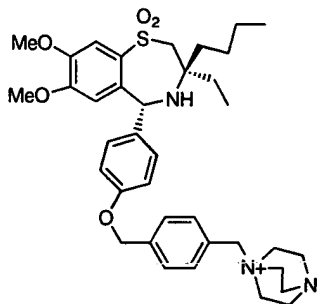


[865] N-[2-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1,1-dioxido-1,5-benzothiazepin-5-yl]phenoxy]ethyl]-N,N-diethylamine (0.29 g, 0.533 mmol) was reacted with 20 eq. EtI, according to the procedure described for PHA-427823E above, to give the desired quat salt (0.200 g/54%). ¹H NMR (CDCl₃) δ 0.77 (t, J = 6.6 Hz, 6H), 1.04-1.21 (m, 8H), 1.36-1.45 (m, 4H), 1.46 (t, J = 7.0 Hz, 9H), 2.84 (s, 6H), 3.10 (s, 2H), 3.57 (q, J = 7.4 Hz, 6H), 3.61 (s, 2H), 4.04 (m, 2H), 4.48 (m, 2H), 5.95 (s, 1H), 6.40 (dd, J = 9.1, 2.2 Hz, 1H), 6.86 (d, J = 8.9 Hz, 2H), 7.07 (d, J = 8.9 Hz, 2H), 7.80 (d, J = 9.1 Hz, 1H). Reverse-phase HPLC: rt = 16.9 min, 95% pure. LC/MS (ES/M - HI): 571.9. Anal Calcd for (C₃₃H₅₄N₃O₃SI): C, 56.64; H, 7.78; N, 6.00; S, 4.58; O, 6.86; I, 18.13. Found: C, 54.94; H, 7.71; N, 5.76; S, 4.58; O, 8.21; I, 18.44.

[866] Various Compounds Made

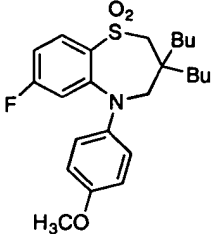
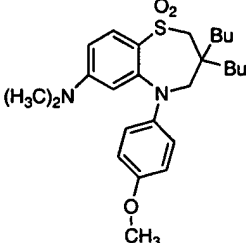
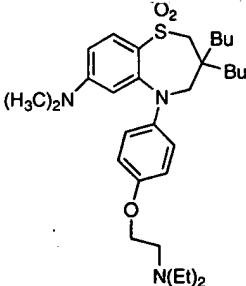
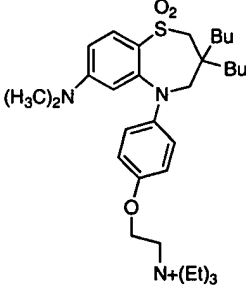
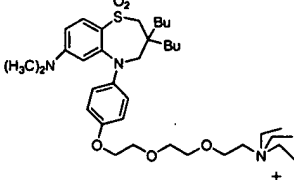
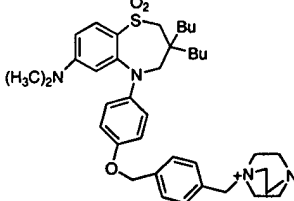
[867] In accordance with the above-described procedures, the following compounds can be/were made:

[868] 1,4 benzathiazapines

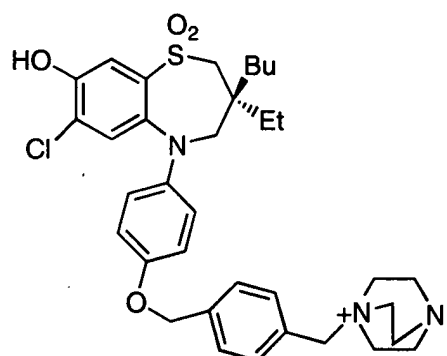
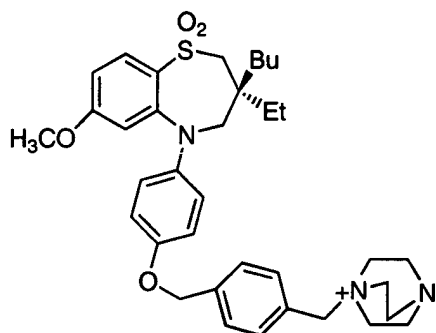
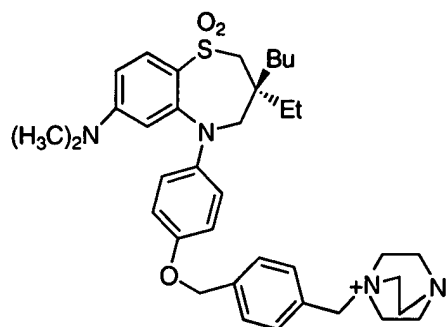


[869] Further, utilizing the biological evaluation procedures outlined below, the IC₅₀ (50% inhibitory concentrations) values indicated in Table 7 below were determined.

Table 7: 1,5-benzothiazepines

Name		IC ₅₀ (uM)
SC- 86288		0.320
SC-86287		0.289 SC- 86436 free phenol 0.21
PHA00400670		26.4
PHA00400884E		> 1
PHA00400885E		0.30
PHA00384640E		0.031

[870] Utilizing the above-noted procedures, the following compounds were prepared:



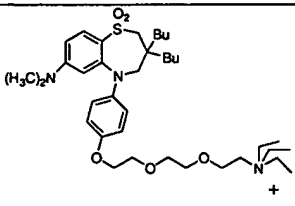
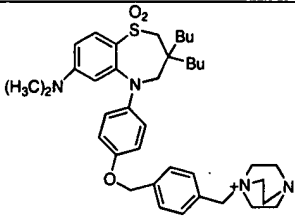
[871] Furthermore, the additional IC₅₀ values were determined as noted in Table 8 below.

Table 8: 1,4 and 1,5 benzothiazipines

compound #	Structure	IC ₅₀ (nanomolar)
1 chiral R,R		600 nM

09912233-07501

compound #	Structure	IC ₅₀ (nanomolar)
2 racemic		497 nM
3 racemic		2092 nM
4 racemic		74 nM
5 racemic		22 nM
6		289 nM
7		15084 nM

compound #	Structure	IC ₅₀ (nanomolar)
8		300 nM
9		30 nM

[872] BIOLOGICAL EVALUATION

[873] The utility of the compounds of the present invention is shown by the following assays. These assays are performed *in vitro* and in animal models essentially using a procedure recognized to show the utility of the present invention.

[874] In Vitro Assay of compounds that inhibit IBAT-mediated uptake of [¹⁴C]-Taurocholate (TC) in H14 Cells

[875] Baby hamster kidney cells (BHK) transfected with the cDNA of human IBAT (H14 cells) are seeded in 96 well Top-Count tissue culture plates at 60,000 cells/well for assays run within 24 hours of seeding, 30,000 cells/well for assays run within 48 hours, and 10,000 cells/well for assays run within 72 hours.

[876] On the day of assay, the cell monolayer is gently washed once with 100 mL assay buffer (Dulbecco's Modified Eagle's medium with 4.5 g/L glucose plus 0.2% (w/v) fatty acid free bovine serum albumin ((FAF)BSA). To each well 50 mL of a two-fold concentrate of test compound in assay buffer is added along with 50 mL of 6 mM [¹⁴C]-taurocholate in assay buffer (final concentration of 3 mM [¹⁴C]-taurocholate). The cell culture plates are incubated 2 hours at 37°C prior to gently washing each well twice with 100 mL 4°C Dulbecco's phosphate-buffered saline (PBS) containing 0.2% (w/v) (FAF)BSA. The wells are then gently washed once with 100 mL 4°C PBS without (FAF)BSA. To each 200 mL of liquid, scintillation counting fluid is added.

The plates are heat sealed and shaken for 30 minutes at room temperature prior to measuring the amount of radioactivity in each well on a Packard Top-Count instrument.

[877] In Vitro Assay of compounds that inhibit uptake of [¹⁴C]-Alanine

[878] The alanine uptake assay is performed in an identical fashion to the taurocholate assay, with the exception that labeled alanine is substituted for the labeled taurocholate.

[879] In Vivo Assay of compounds that inhibit Rat Ileal uptake of [¹⁴C]-Taurocholate into Bile

[880] (See Une et al. "Metabolism of 3a,7β-dihydroxy-7β-methyl-5β-cholanoic acid and 3a,7β-dihydroxy-7a-methyl-5β-cholanoic acid in hamsters", *Biochimica et Biophysica Acta*, Vol. 833, pp. 196-202 (1985)).

[881] Male wistar rats (200-300 g) are anesthetized with inactin @100 mg/kg. Bile ducts are cannulated with a 10" length of PE10 tubing. The small intestine is exposed and laid out on a gauze pad. A canulae (1/8" luer lock, tapered female adapter) is inserted at 12 cm from the junction of the small intestine and the cecum. A slit is cut at 4 cm from this same junction (utilizing a 8 cm length of ileum). 20 mL of warm Dulbecco's phosphate buffered saline, pH 6.5 ("PBS") is used to flush out the intestine segment. The distal opening is cannulated with a 20 cm length of silicone tubing (0.02" I.D. x 0.037" O.D.). The proximal cannulae is hooked up to a peristaltic pump and the intestine is washed for 20 minutes with warm PBS at 0.25 ml/minute. Temperature of the gut segment is monitored continuously.

[882] At the start of the experiment, 2.0 mL of control sample ([¹⁴C]-taurocholate @ 0.05 mi/mL with 5 mM cold taurocholate) is loaded into the gut segment with a 3 mL syringe and bile sample collection is begun. Control sample is infused at a rate of 0.25 ml/minute for 21 minutes. Bile samples fractions are collected every 3 minutes for the first 27 minutes of the procedure. After the 21 minutes of sample infusion, the ileal loop is washed out with 20 mL of warm PBS (using a 30 mL syringe), and then the loop is washed out for 21 minutes with warm PBS at 0.25 ml/minutes. A second

perfusion is initiated as described above but with test compound being administered as well (21 minutes administration followed by 21 minutes of wash out) and bile sampled every 3 minutes for the first 27 minutes. If necessary, a third perfusion is performed as above that typically contains the control sample.

[883] Measurement of Hepatic Cholesterol Concentration (HEPATIC CHOL)

[884] Liver tissue is weighed and homogenized in chloroform:methanol (2:1). After homogenization and centrifugation the supernatant is separated and dried under nitrogen. The residue is dissolved in isopropanol and the cholesterol content is measured enzymatically, using a combination of cholesterol oxidase and peroxidase, as described by Allain, C. A., et al. (1974) *Clin. Chem.* **20**, 470.

[885] Measurement of Hepatic HMG CoA-Reductase Activity (HMG COA)

[886] Hepatic microsomes are prepared by homogenizing liver samples in a phosphate/sucrose buffer, followed by centrifugal separation. The final pelleted material is resuspended in buffer and an aliquot is assayed for HMG CoA reductase activity by incubating for 60 minutes at 37° C in the presence of ¹⁴C-HMG-CoA (Dupont-NEN). The reaction is stopped by adding 6N HCl followed by centrifugation. An aliquot of the supernatant is separated, by thin-layer chromatography, and the spot corresponding to the enzyme product is scraped off the plate, extracted and radioactivity is determined by scintillation counting. (Reference: Akerlund, J. and Bjorkhem, I. (1990) *J. Lipid Res.* **31**, 2159).

[887] Determination of Serum Cholesterol (SER.CHOL, HDL-CHOL, TGI and VLDL + LDL)

[888] Total serum cholesterol (SER.CHOL) is measured enzymatically using a commercial kit from Wako Fine Chemicals (Richmond, VA); Cholesterol C11, Catalog No. 276-64909. HDL cholesterol (HDL-CHOL) is assayed using this same kit after precipitation of VLDL and LDL with Sigma Chemical Co. HDL Cholesterol reagent, Catalog No. 352-3 (dextran sulfate method). Total serum triglycerides (blanked) (TGI) are assayed enzymatically with Sigma Chemical Co. GPO-Trinder, Catalog No.

337-B. VLDL and LDL (VLDL + LDL) cholesterol concentrations are calculated as the difference between total and HDL cholesterol.

[889] Measurement of Hepatic Cholesterol 7 α -Hydroxylase Activity (7 α -OHase)

[890] Hepatic microsomes are prepared by homogenizing liver samples in a phosphate/sucrose buffer, followed by centrifugal separation. The final pelleted material is resuspended in buffer and an aliquot is assayed for cholesterol 7 α -hydroxylase activity by incubating for 5 minutes at 37° C in the presence of NADPH. Following extraction into petroleum ether, the organic solvent is evaporated and the residue is dissolved in acetonitrile/ methanol. The enzymatic product is separated by injecting an aliquot of the extract onto a C₁₈ reversed phase HPLC column and quantitating the eluted material using UV detection at 240 nm. (Reference: Horton, J. D., et al. (1994) *J. Clin. Invest.* **93**, 2084).

[891] Rat Gavage Assay

[892] Male Wister rats (275-300 g) are administered IBAT inhibitors using an oral gavage procedure. Drug or vehicle (0.2% Tween 80 in water) is administered once a day (9:00-10:00 a.m.) for 4 days at varying dosages in a final volume of 2 mL per kilogram of body weight. Total fecal samples are collected during the final 48 hours of the treatment period and analyzed for bile acid content using an enzymatic assay as described below. Compound efficacy is determined by comparison of the increase in fecal bile acid (FBA) concentration in treated rats to the mean FBA concentration of rats in the vehicle group.

[893] Measurement of Fecal Bile Acid Concentration (FBA)

[894] Total fecal output from individually housed hamsters is collected for 24 or 48 hours, dried under a stream of nitrogen, pulverized and weighed. Approximately 0.1 gram is weighed out and extracted into an organic solvent (butanol/water). Following separation and drying, the residue is dissolved in methanol and the amount of bile acid present is measured enzymatically using the 3 α -hydroxysteroid steroid dehydrogenase reaction with bile acids to reduce NAD. (Reference: Mashige, F., et al. (1981) *Clin. Chem.* **27**, 1352).

[895] [³H]taurocholate Uptake in Rabbit Brush Border Membrane Vesicles (BBMV)

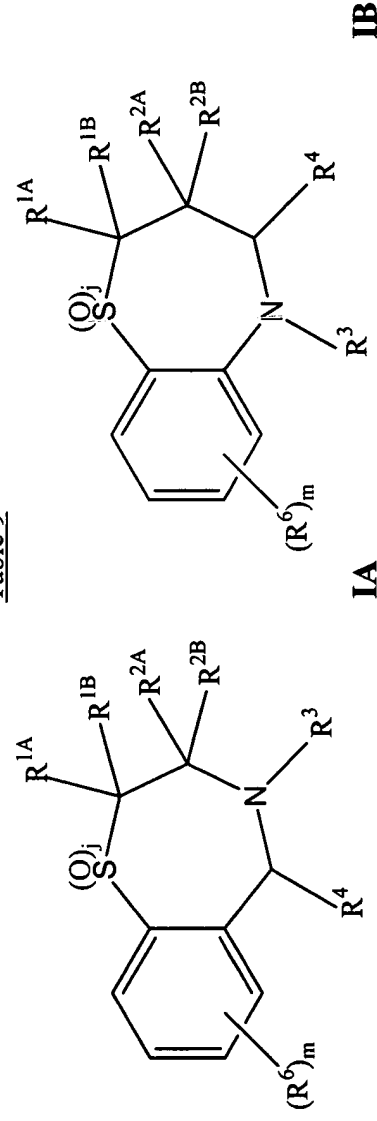
[896] Rabbit Ileal brush border membranes are prepared from frozen ileal mucosa by the calcium precipitation method describe by Malathi et al. (Reference: (1979) *Biochimica Biophysica Acta*, **554**, 259). The method for measuring taurocholate is essentially as described by Kramer et al. (Reference: (1992) *Biochimica Biophysica Acta*, **1111**, 93) except the assay volume is 200 µL instead of 100 µL. Briefly, at room temperature a 190 µL solution containing 2µM [³H]-taurocholate (0.75 µCi), 20 mM tris, 100 mM sodium chloride, 100 mM mannitol pH 7.4 is incubated for 5 seconds with 10 µL of brush border membrane vesicles (60-120 µg protein). The incubation is initiated by the addition of the BBMV while vortexing and the reaction is stopped by the addition of 5 mL of ice cold buffer (20 mM Hepes-tris, 150 mM KCl) followed immediately by filtration through a nylon filter (0.2 µm pore) and an additional 5 mL wash with stop buffer.

[897] Acyl-CoA; Cholesterol Acyl Transferase (ACAT)

[898] Hamster liver and rat intestinal microsomes are prepared from tissue as described previously (Reference: (1980) *J. Biol. Chem.* **255**, 9098) and used as a source of ACAT enzyme. The assay consists of a 2.0 mL incubation containing 24 µM Oleoyl-CoA (0.05 µCi) in a 50 mM sodium phosphate, 2 mM DTT pH 7.4 buffer containing 0.25 % BSA and 200 µg of microsomal protein. The assay is initiated by the addition of oleoyl-CoA. The reaction is allowed to proceed for 5 minutes at 37°C and is terminated by the addition of 8.0 mL of chloroform/ methanol (2:1). To the extraction is added 125 µg of cholesterol oleate in chloroform methanol to act as a carrier and the organic and aqueous phases of the extraction are separated by centrifugation after thorough vortexing. The chloroform phase is taken to dryness and then spotted on a silica gel 60 thin layer chromatography plate and developed in hexane/ethyl ether (9:1). The amount of cholesterol ester formed is determined by measuring the amount of radioactivity incorporated into the cholesterol oleate spot on the thin layer chromatography plate with a Packard instaimager.

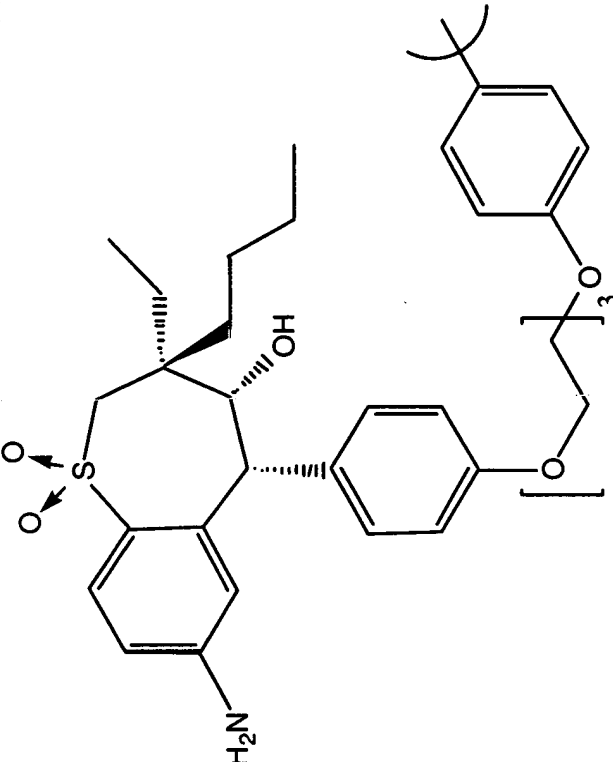
[899] Various additional compounds noted in Tables 9-10 below can be/were made according to the procedures outlined above.

Table 9



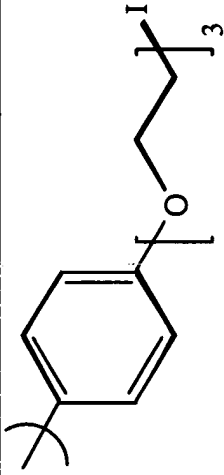
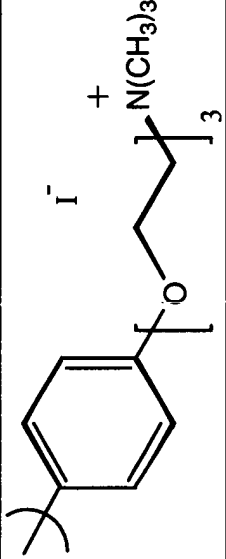
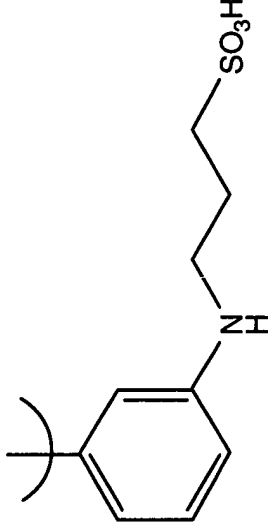
$R^{1A} = R^{1B} = H$; R^3 or R^4 independently = R^5

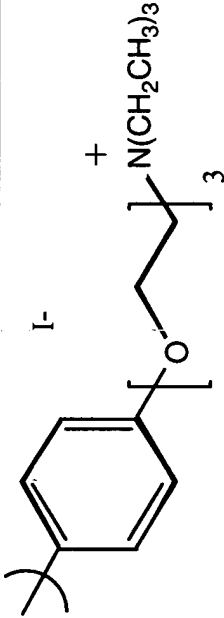
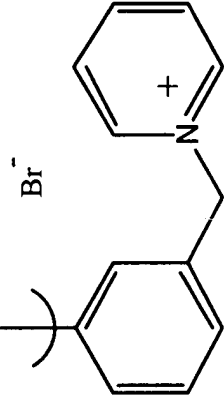
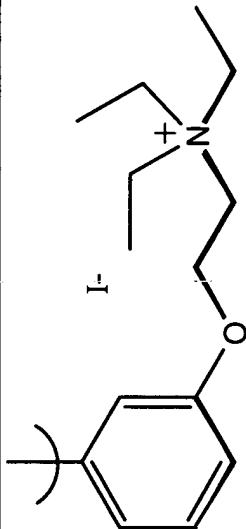
Compound Number	R^{2A}	R^{2B}	R^5
101	ethyl	n-butyl	phenyl
102	ethyl	n-butyl	phenyl
103	n-butyl	Ethyl	phenyl
104	ethyl	n-butyl	phenyl
105	ethyl	n-butyl	phenyl
106	ethyl	n-butyl	phenyl
107	n-butyl	Ethyl	4-(decyloxy)phenyl
108	ethyl	n-butyl	phenyl
109	ethyl	n-butyl	4-(decyloxy)phenyl

Compound Number	R ^{2A}	R ^{2B}	R ⁵
110	ethyl	n-butyl	phenyl
111	n-butyl	Ethyl	4-hydroxyphenyl
112	ethyl	n-butyl	
113	ethyl	n-butyl	4-hydroxyphenyl
114	ethyl	n-butyl	4-methoxyphenyl
115	n-butyl	ethyl	4-methoxyphenyl
116	ethyl	n-butyl	4-methoxyphenyl
117	n-butyl	ethyl	phenyl
118	ethyl	n-butyl	phenyl
119	ethyl	n-butyl	phenyl

Compound Number	R ^{2A}	R ^{2B}	R ⁵
120	n-butyl	ethyl	phenyl
121	ethyl	n-butyl	phenyl
122	n-butyl	ethyl	phenyl
123	ethyl	n-butyl	phenyl
124	n-butyl	ethyl	phenyl
125	ethyl	n-butyl	phenyl
126	n-butyl	ethyl	4-fluorophenyl
127	n-butyl	ethyl	4-fluorophenyl
128	Ethyl	n-butyl	4-fluorophenyl
129	Ethyl	n-butyl	4-fluorophenyl
131	Ethyl	n-butyl	4-fluorophenyl
132	Ethyl	n-butyl	phenyl
133	Ethyl	n-butyl	phenyl
134	Ethyl	n-butyl	phenyl
135	Ethyl	n-butyl	phenyl
136	Ethyl	n-butyl	phenyl
137	n-butyl	ethyl	phenyl
138	n-butyl	ethyl	phenyl
139	n-butyl	ethyl	phenyl
140			
141			
142	Ethyl	n-butyl	H
143	Ethyl	n-butyl	3-methoxyphenyl
144	Ethyl	n-butyl	4-fluorophenyl
262	Ethyl	n-butyl	3-methoxyphenyl
263	Ethyl	n-butyl	H

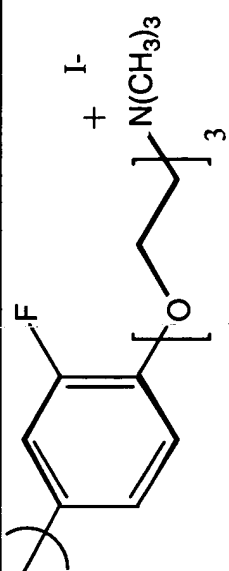
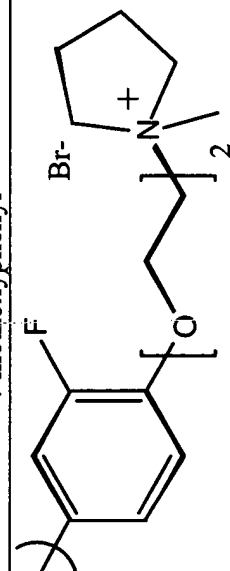
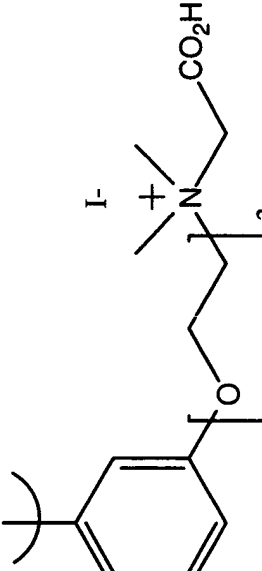
Compound Number	R ^{2A}	R ^{2B}	R ⁵
264	Ethyl	n-butyl	3-trifluoromethylphenyl
265	Ethyl	n-butyl	H
266	Ethyl	n-butyl	3-hydroxyphenyl
267	Ethyl	n-butyl	3-hydroxyphenyl
268	Ethyl	n-butyl	4-fluorophenyl
269	Ethyl	n-butyl	H
270	Ethyl	n-butyl	4-fluorophenyl
271	Ethyl	n-butyl	3-methoxyphenyl
272	Ethyl	n-butyl	H
273	Ethyl	n-butyl	H
274	Ethyl	n-butyl	4-fluorophenyl
275	Ethyl	n-butyl	H
276	Ethyl	n-butyl	3-methoxyphenyl
277	Ethyl	n-butyl	3-fluorophenyl
278	Ethyl	n-butyl	2-fluorophenyl
279	Ethyl	n-butyl	3-fluorophenyl
280	Ethyl	n-butyl	2-fluorophenyl
281	Ethyl	n-butyl	4-fluorophenyl
282	Ethyl	n-butyl	4-fluorophenyl
283	Ethyl	n-butyl	H
284	Ethyl	n-butyl	4-fluorophenyl
286	Ethyl	ethyl	phenyl
287	Ethyl	ethyl	phenyl
288	methyl	methyl	phenyl
289	n-butyl	n-butyl	phenyl
290	n-butyl	n-butyl	phenyl

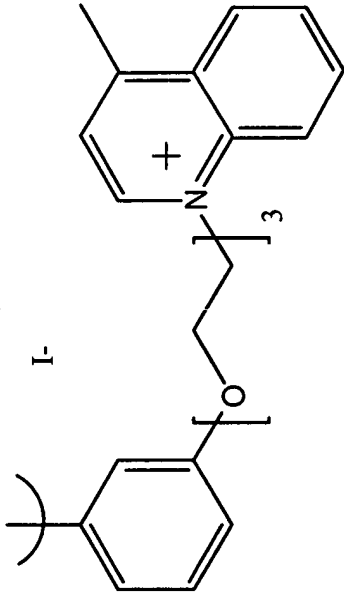
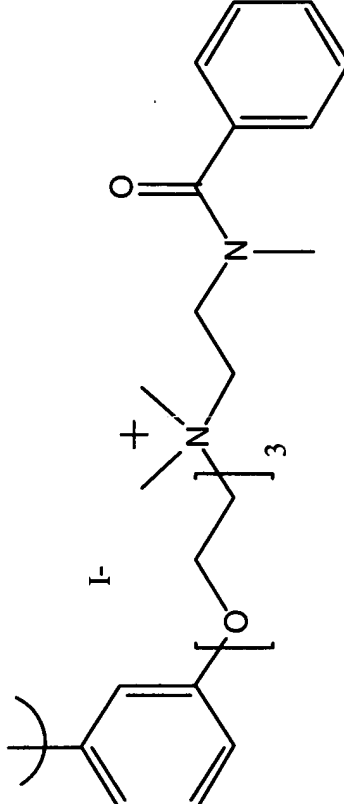
Compound Number	R ^{2A}	R ^{2B}	R ⁵
291	n-butyl	n-butyl	phenyl
292	n-butyl	n-butyl	4-fluorophenyl
293	n-butyl	n-butyl	phenyl
294	n-butyl	n-butyl	phenyl
295	Ethyl	n-butyl	
296	Ethyl	n-butyl	
1000	Ethyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1001	Ethyl	n-butyl	
1002	Ethyl	n-butyl	
1003	Ethyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1004	Ethyl	n-butyl	<p>CF₃COO- + (CH₃CH₂)₃N⁺</p>
1005	n-butyl	n-butyl	<p>CF₃COO- + (CH₃CH₂)₃N⁺</p>
1006	n-butyl	n-butyl	<p>Br-</p>

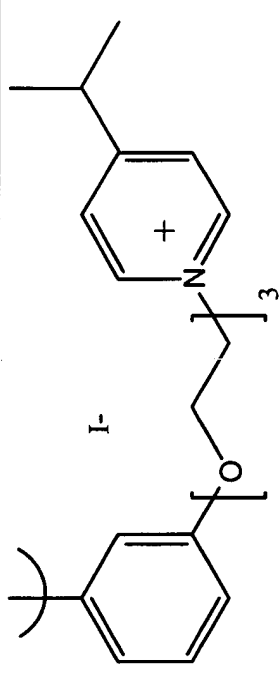
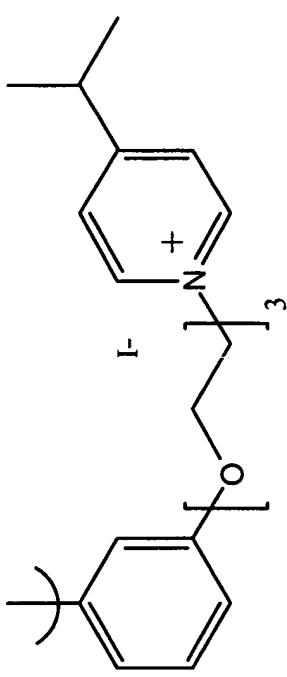
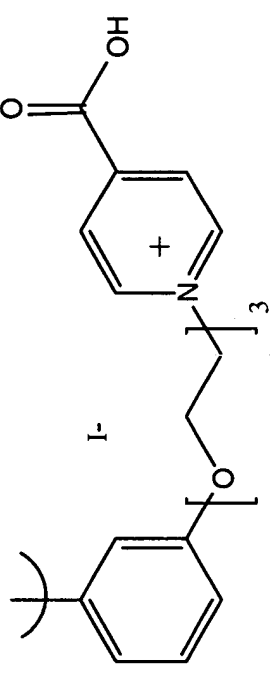
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1007	n-butyl	n-butyl	
1008	n-butyl	n-butyl	
1009	n-butyl	n-butyl	
1010	n-butyl	n-butyl	3-fluoro-4-methoxyphenyl
1011	n-butyl	n-butyl	3-fluoro-4-(5-triethylammoniumpentyloxy)phenyl, trifluoroacetate salt

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1012	n-butyl	n-butyl	4-hydroxyphenyl
1013	n-butyl	n-butyl	
1014	n-butyl	n-butyl	4-methoxyphenyl
1015	n-butyl	n-butyl	
1016	n-butyl	n-butyl	

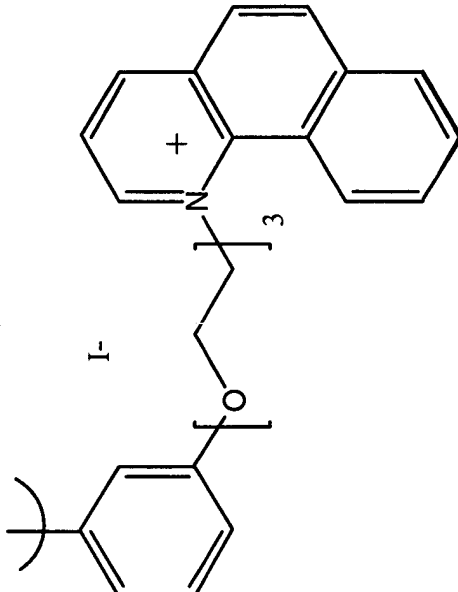
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1017	n-butyl	n-butyl	
1018	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1019	n-butyl	n-butyl	
1020	n-butyl	n-butyl	
1021	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1022	n-butyl	n-butyl	
1023	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1026	n-butyl	n-butyl	
1027	n-butyl	n-butyl	
1028	n-butyl	n-butyl	

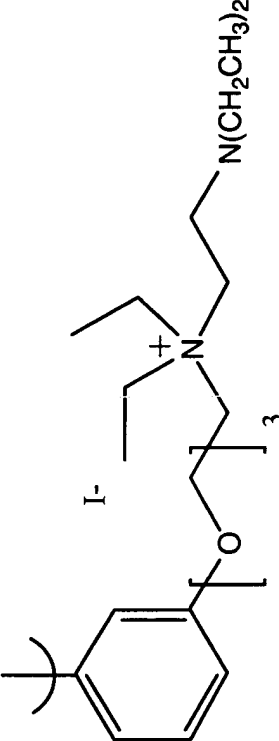
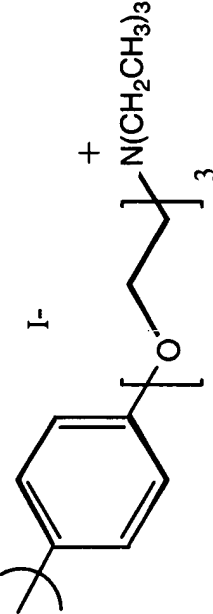
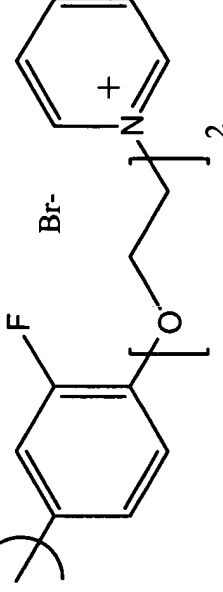
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1029	n-butyl	n-butyl	
1030	n-butyl	n-butyl	
1031	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1034	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1035	n-butyl	n-butyl	
1036	n-butyl	n-butyl	
1037	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1038	n-butyl	n-butyl	
1039	n-butyl	n-butyl	phenyl
1040	n-butyl	n-butyl	
1041	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1042	n-butyl	n-butyl	
1043	n-butyl	n-butyl	
1044	n-butyl	n-butyl	
1045	n-butyl	n-butyl	

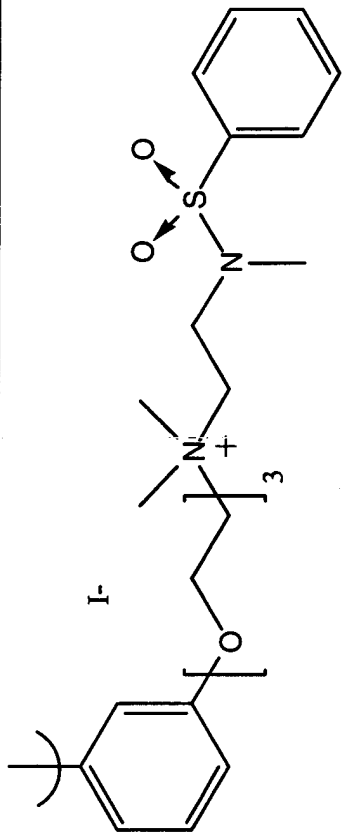
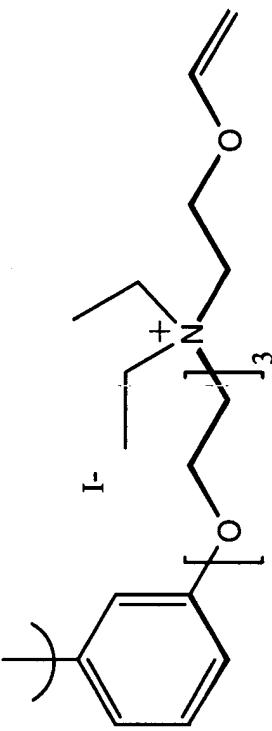
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1046	n-butyl	n-butyl	3-aminophenyl
1047	n-butyl	n-butyl	
1048	n-butyl	n-butyl	
1049	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1050	n-butyl	n-butyl	
1051	n-butyl	n-butyl	
1052	n-butyl	n-butyl	

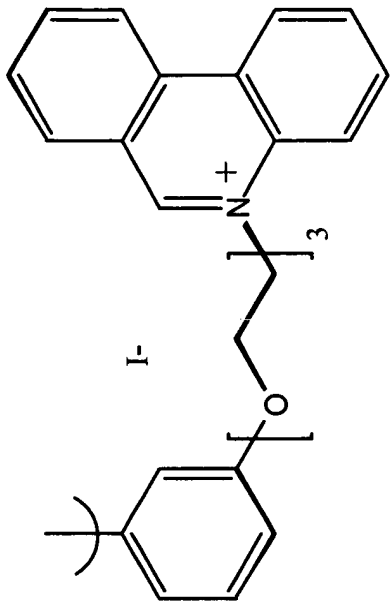
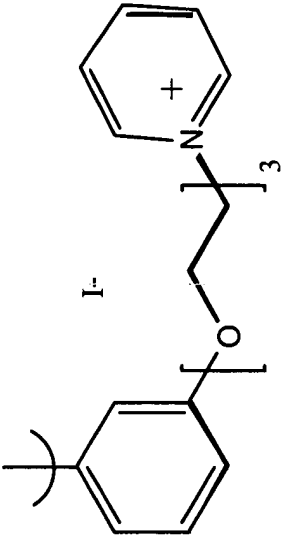
Compound Number	R ^{2A}	R ^{2B}	R ⁵
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1054	n-butyl	n-butyl	

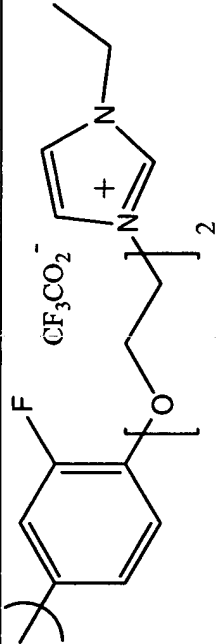
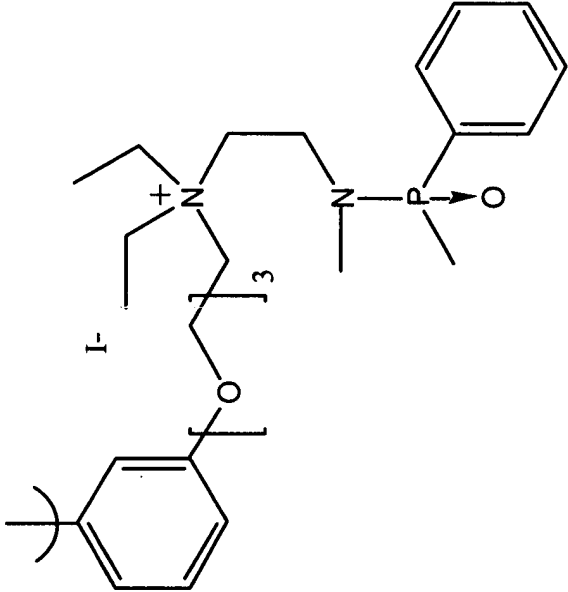
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1055	n-butyl	n-butyl	
1056	n-butyl	n-butyl	
1057	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1058	n-butyl	n-butyl	
1059	n-butyl	n-butyl	
1060	Ethyl	n-butyl	3-fluoro-4-methoxyphenyl
1061	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1062	n-butyl	n-butyl	
1063	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1064	n-butyl	n-butyl	
1065	n-butyl	n-butyl	

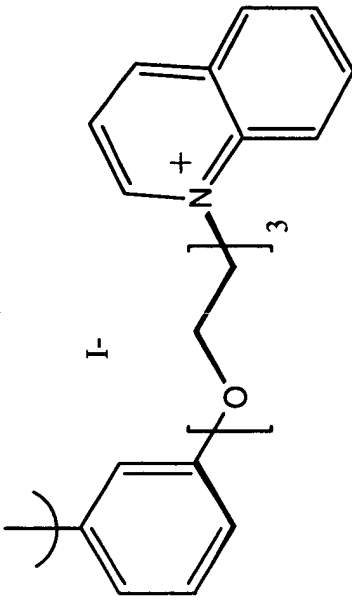
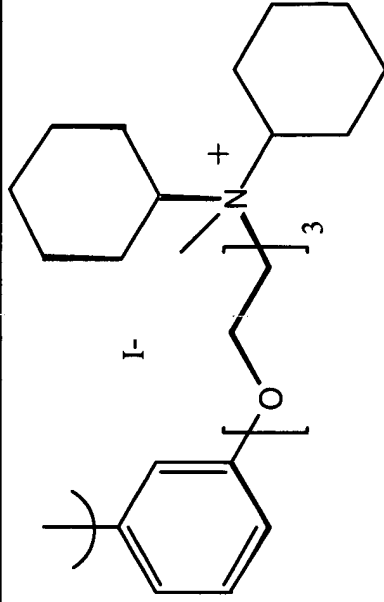
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1066	n-butyl	n-butyl	
1067	n-butyl	n-butyl	thiophen-3-yl
1068	n-butyl	n-butyl	
1069	n-butyl	n-butyl	phenyl

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1070	n-butyl	n-butyl	
1071	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1072	n-butyl	n-butyl	
1073	n-butyl	n-butyl	
1074	Ethyl	n-butyl	3-fluoro-4-methoxyphenyl
1075	n-butyl	n-butyl	4-fluorophenyl
1076	n-butyl	n-butyl	
1077	n-butyl	n-butyl	3-hydroxymethylphenyl
1078	Ethyl	n-butyl	4-hydroxyphenyl

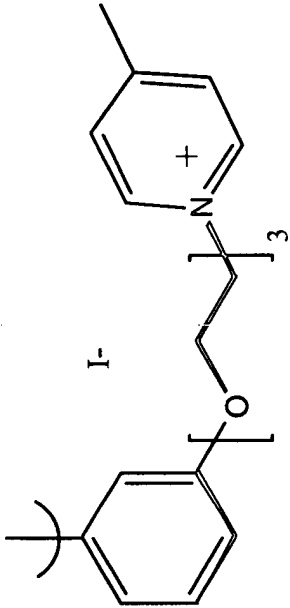
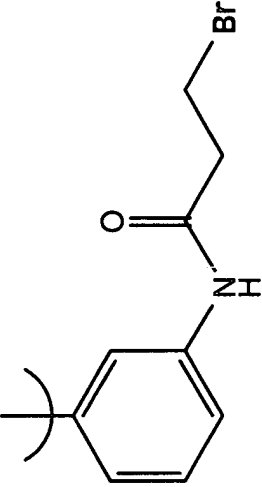
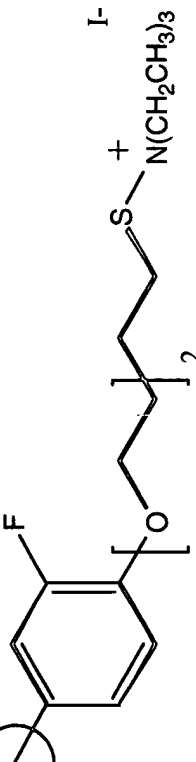
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1080	n-butyl	n-butyl	
1081	n-butyl	n-butyl	
1082	n-butyl	n-butyl	2-pyridyl
1083	n-butyl	n-butyl	

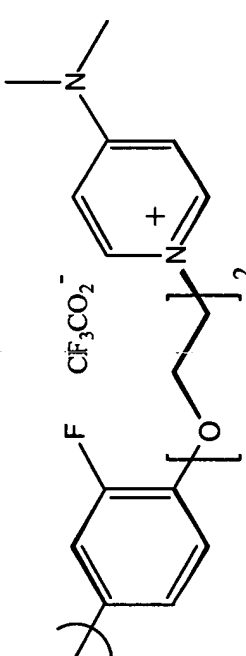
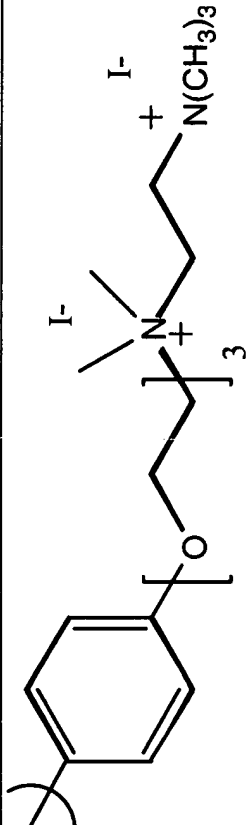
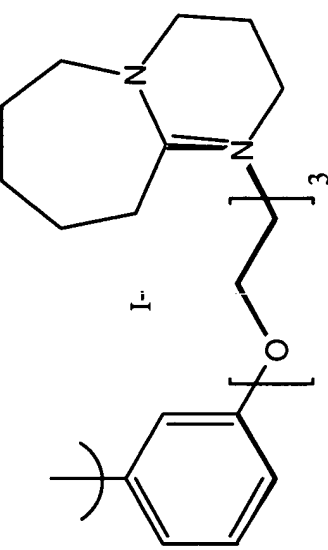
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1084	n-butyl	n-butyl	
1085	n-butyl	n-butyl	thiophen-3-yl
1086	n-butyl	n-butyl	
1087	n-butyl	n-butyl	

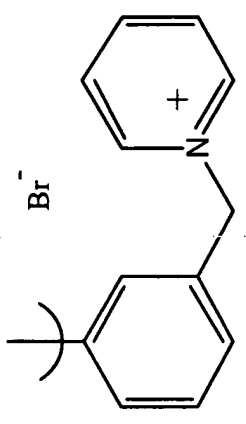
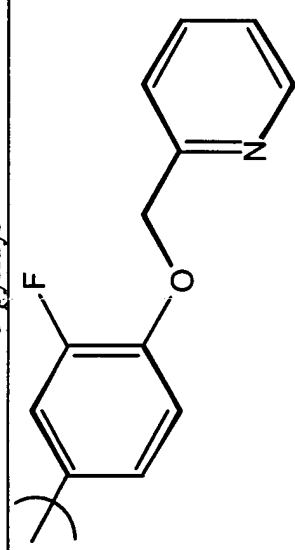
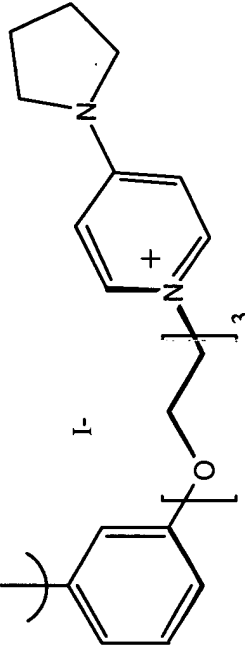
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1088	Ethyl	n-butyl	
1089	Ethyl	n-butyl	
1090	n-butyl	n-butyl	
1091	n-butyl	n-butyl	

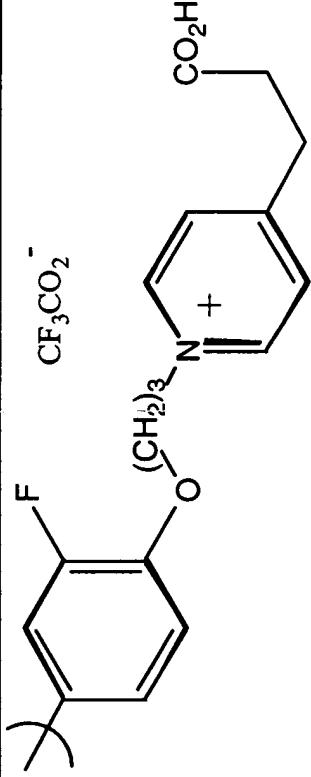
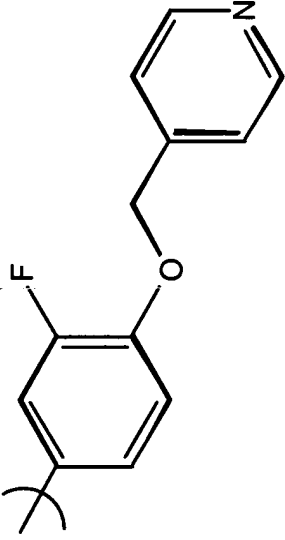
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1092	n-butyl	n-butyl	
1093	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1094	n-butyl	n-butyl	
1095	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1096	n-butyl	n-butyl	
1097	n-butyl	n-butyl	
1098	n-butyl	n-butyl	
1099	Ethyl	n-butyl	4-methoxyphenyl
1100	n-butyl	n-butyl	4-methoxyphenyl

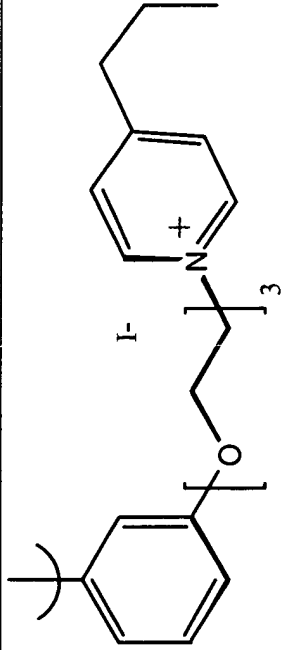
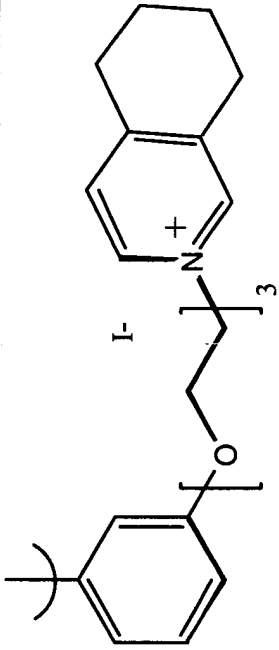
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1101	n-butyl	n-butyl	
1102	n-butyl	n-butyl	3-carboxymethyl/phenyl
1103	n-butyl	n-butyl	
1104	n-butyl	n-butyl	
1105	n-butyl	n-butyl	5-piperonyl
1106	n-butyl	n-butyl	3-hydroxyphenyl

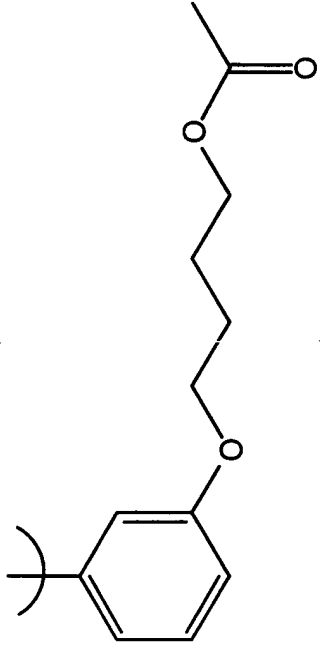
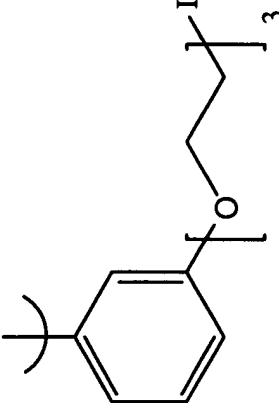
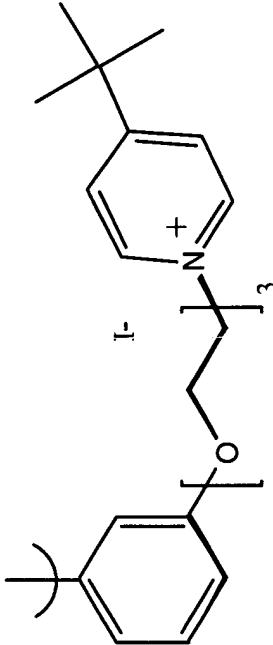
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1107	n-butyl	n-butyl	
1108	n-butyl	n-butyl	3-pyridyl
1109	n-butyl	n-butyl	
1110	n-butyl	n-butyl	

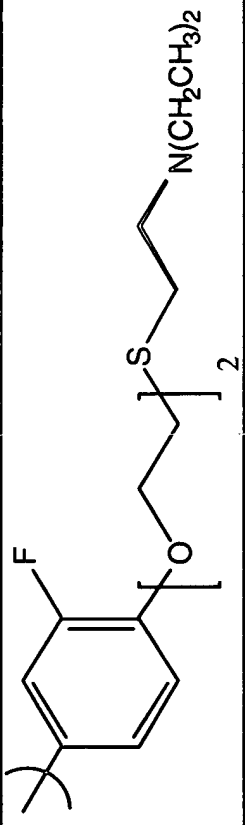
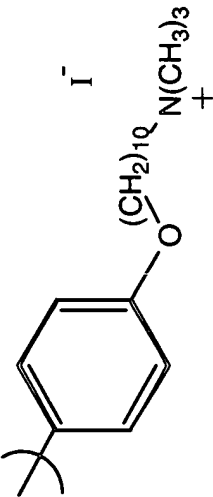
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1111	n-butyl	n-butyl	
1112	n-butyl	n-butyl	4-pyridyl
1113	n-butyl	n-butyl	
1114	n-butyl	n-butyl	3-methoxyphenyl
1115	n-butyl	n-butyl	4-fluorophenyl
1116	Ethyl	n-butyl	3-tolyl

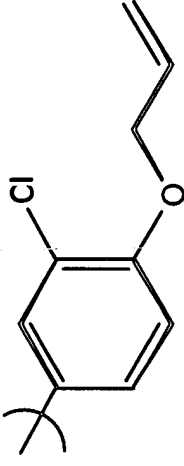
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1117	Ethyl	n-butyl	
1118	Ethyl	n-butyl	3-fluoro-4-hydroxyphenyl
1119	n-butyl	n-butyl	
1120	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1121	n-butyl	n-butyl	
1122	n-butyl	n-butyl	
1123	n-butyl	n-butyl	phenyl
1124	n-butyl	n-butyl	3-methoxyphenyl
1125	n-butyl	n-butyl	3-chloro-4-methoxyphenyl
1126	Ethyl	n-butyl	

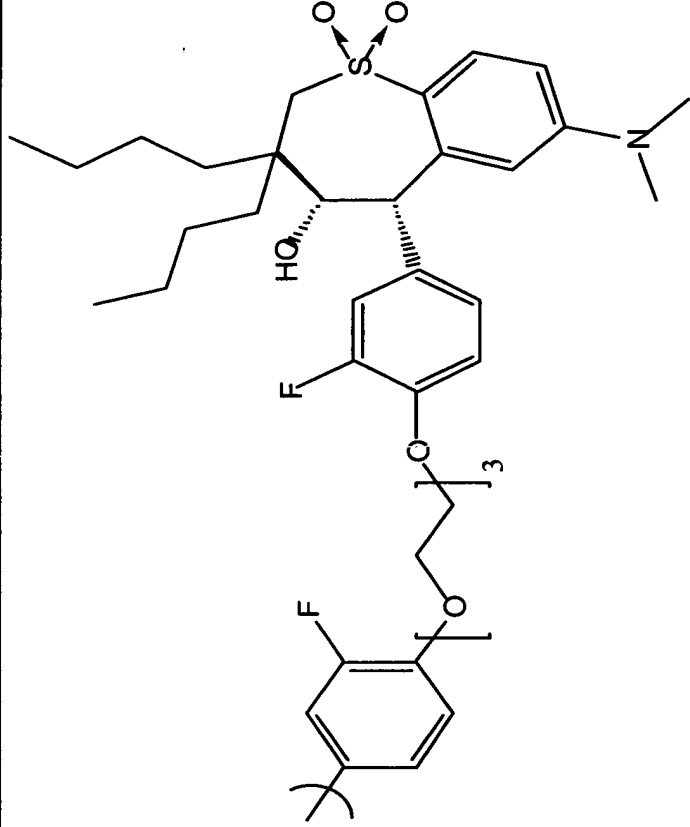
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1127	n-butyl	n-butyl	
1128	n-butyl	n-butyl	3-fluoro-4-hydroxyphenyl
1129	n-butyl	n-butyl	4-fluorophenyl
1130	n-butyl	n-butyl	3-chloro-4-fluorophenyl
1131	Ethyl	n-butyl	4-methoxyphenyl
1132	n-butyl	n-butyl	
1133	n-butyl	n-butyl	4-cyanomethylphenyl

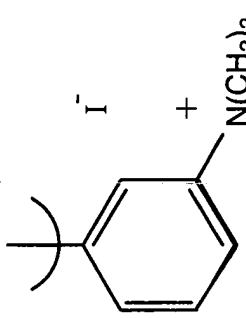
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1134	Ethyl	n-butyl	
1135	n-butyl	n-butyl	3,4-dimethoxyphenyl
1136	n-butyl	n-butyl	
1137	n-butyl	n-butyl	4-fluorophenyl
1138	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1139	n-butyl	n-butyl	3,4-difluorophenyl
1140	n-butyl	n-butyl	3-methoxyphenyl
1141	n-butyl	n-butyl	4-fluorophenyl
1142	n-butyl	n-butyl	
1143	n-butyl	n-butyl	H
1144	n-butyl	n-butyl	5-piperonyl
1145	n-butyl	n-butyl	4-methoxyphenyl
1146	n-butyl	n-butyl	
1147	n-butyl	n-butyl	3-methoxyphenyl
1148	n-butyl	n-butyl	4-fluorophenyl
1149	n-butyl	n-butyl	4-fluorophenyl
1150	n-butyl	n-butyl	3-methoxyphenyl
1151	n-butyl	ethyl	3-fluoro-4-methoxyphenyl
1152	n-butyl	n-butyl	phenyl
1153	n-butyl	n-butyl	4-fluorophenyl
1154	n-butyl	n-butyl	3-methoxyphenyl

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1155	n-butyl	n-butyl	4-fluorophenyl
1156	n-butyl	n-butyl	4-fluorophenyl
1157	n-butyl	n-butyl	4-fluorophenyl
1158	n-butyl	n-butyl	4-pyridinyl, hydrochloride salt
1159	n-butyl	ethyl	phenyl
1160	n-butyl	n-butyl	4-fluorophenyl
1161	n-butyl	n-butyl	3,5-dichloro-4-methoxyphenyl
1162	n-butyl	n-butyl	phenyl
1163	n-butyl	n-butyl	3-(dimethylamino)phenyl
1164	n-butyl	n-butyl	4-pyridinyl
1165	n-butyl	n-butyl	3-fluoro-4-methoxyphenyl
1166	n-butyl	n-butyl	3-hydroxyphenyl
1167	n-butyl	n-butyl	
1168	n-butyl	n-butyl	4-hydroxyphenyl
1169	n-butyl	n-butyl	phenyl
1170	n-butyl	n-butyl	3-methoxyphenyl
1171	n-butyl	n-butyl	4-(trifluoromethylsulfonyloxy)phenyl
1172	n-butyl	n-butyl	4-pyridinyl
1173	n-butyl	n-butyl	4-fluorophenyl
1174	Ethyl	n-butyl	3-methoxyphenyl
1175	Ethyl	n-butyl	3-methoxyphenyl
1176	n-butyl	n-butyl	4-fluorophenyl

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1177	n-butyl	n-butyl	3-methoxyphenyl
1178	n-butyl	n-butyl	3-(trifluoromethyl)sulfonyloxyphenyl
1179	n-butyl	n-butyl	phenyl
1180	n-butyl	n-butyl	phenyl
1181	n-butyl	n-butyl	4-fluorophenyl
1182	n-butyl	n-butyl	4-(dimethylamino)phenyl
1183	n-butyl	n-butyl	3-methoxyphenyl
1184	n-butyl	n-butyl	4-fluorophenyl
1185	n-butyl	n-butyl	4-fluorophenyl
1186	n-butyl	n-butyl	phenyl
1187	n-butyl	n-butyl	4-fluorophenyl
1188	n-butyl	n-butyl	4-methoxyphenyl
1189	n-butyl	n-butyl	3,4-difluorophenyl
1190	n-butyl	n-butyl	2-bromophenyl
1191	n-butyl	n-butyl	4-(dimethylamino)phenyl
1192	n-butyl	n-butyl	3-(dimethylamino)phenyl
1193	n-butyl	n-butyl	4-(2-(2-methylpropyl))phenyl

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1194	n-butyl	n-butyl	
1195	n-butyl	n-butyl	4-methoxyphenyl

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1196	n-butyl	n-butyl	
1197	n-butyl	ethyl	phenyl
1198	n-butyl	n-butyl	4-(pyridinyl-N-oxide)

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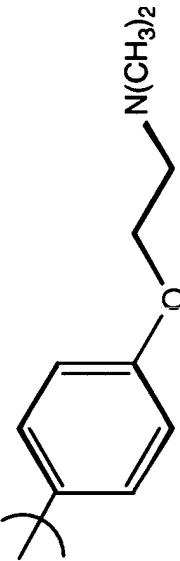
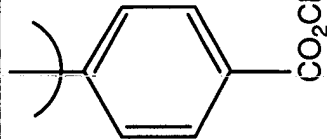
Compound Number	R ^{2A}	R ^{2B}	R ^S
1199	n-butyl	n-butyl	
1200	n-butyl	n-butyl	H
1201	n-butyl	n-butyl	H

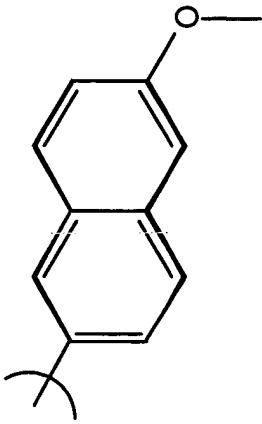
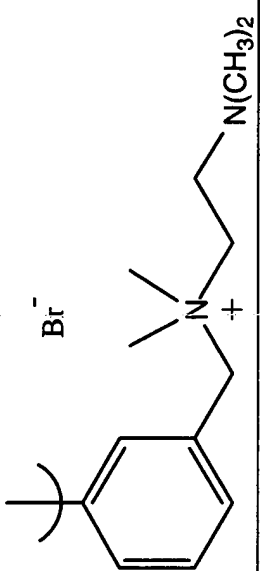
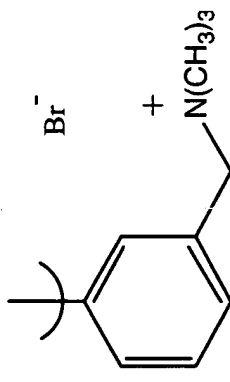
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1202	n-butyl	n-butyl	 $\text{N}(\text{CH}_3)_3^+$
1203	n-butyl	n-butyl	5-piperazinyl
1204	n-butyl	n-butyl	4-fluorophenyl
1205	n-butyl	n-butyl	
1206	n-butyl	n-butyl	 Br^-
1207	n-butyl	n-butyl	 Br^-

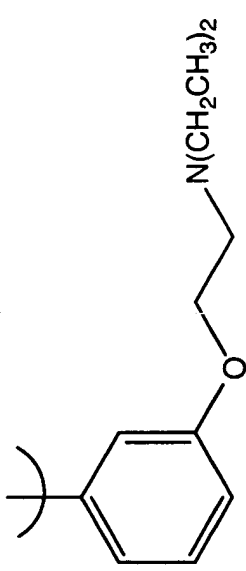
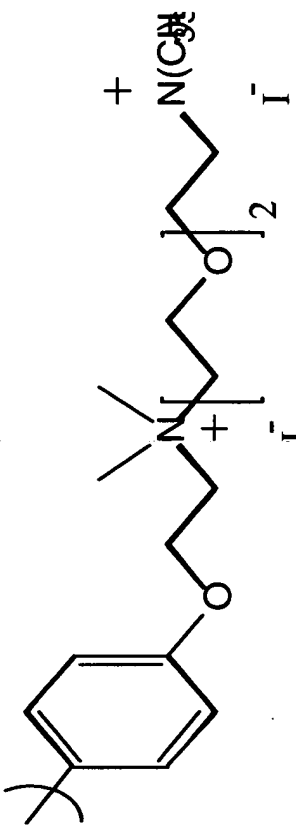
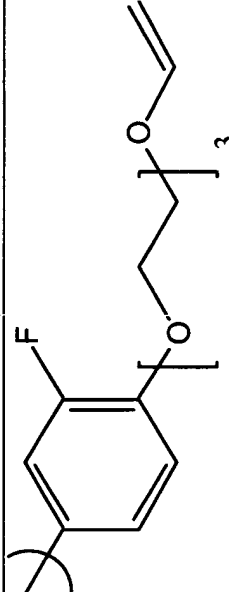
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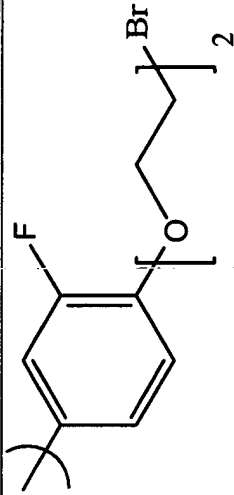
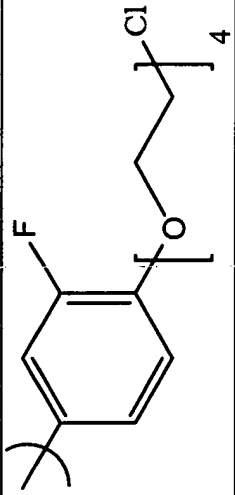
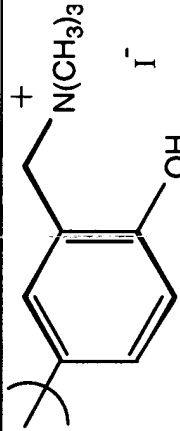
Compound Number	R ^{2A}	R ^{2B}	R ^S
1208	n-butyl	n-butyl	4-methoxyphenyl
1209	n-butyl	n-butyl	phenyl
1210	n-butyl	n-butyl	2-(dimethylamino)phenyl
1211	Ethyl	n-butyl	
1212	n-butyl	n-butyl	4-methoxyphenyl
1213	n-butyl	ethyl	H
1214	n-butyl	ethyl	phenyl
1215	n-butyl	n-butyl	4-methoxyphenyl
1216	Ethyl	n-butyl	5-piperonyl

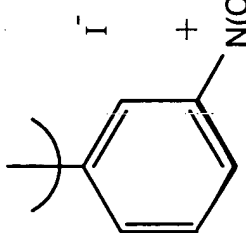
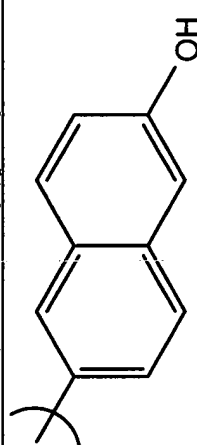
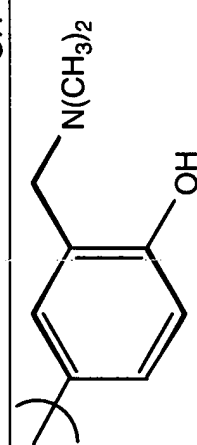
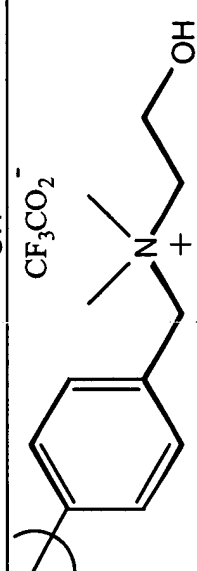
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Compound Number	R ^{2A}	R ^{2B}	R ⁵
1217	n-butyl	n-butyl	4-carboxyphenyl
1218	n-butyl	n-butyl	4-methoxyphenyl
1219	n-butyl	n-butyl	
1220	n-butyl	n-butyl	3-methoxyphenyl
1221	n-butyl	n-butyl	
1222	n-butyl	n-butyl	3-methoxyphenyl
1223	n-butyl	n-butyl	phenyl
1224	n-butyl	n-butyl	3-nitrophenyl
1225	n-butyl	ethyl	3-methylphenyl
1226	Ethyl	n-butyl	5-piperonyl
1227	n-butyl	n-butyl	4-fluorophenyl
1228	n-butyl	n-butyl	2-pyrrolyl
1229	n-butyl	n-butyl	3-chloro-4-hydroxyphenyl
1230	n-butyl	n-butyl	phenyl

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1231	n-butyl	n-butyl	
1232	n-butyl	n-butyl	3-thiophenyl
1233	n-butyl	n-butyl	
1234	n-butyl	n-butyl	

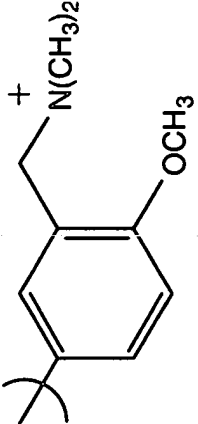
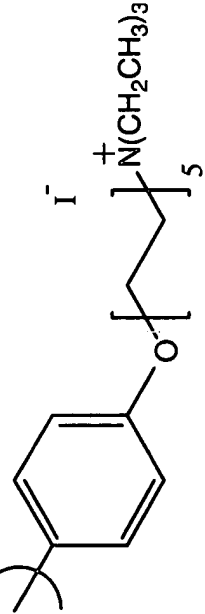
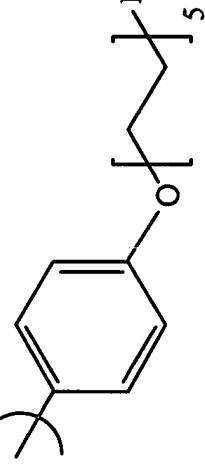
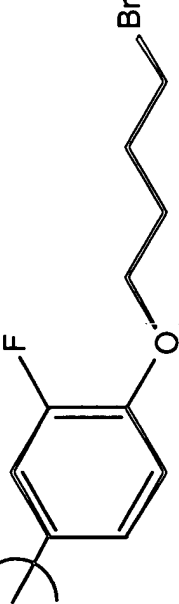
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1235	n-butyl	n-butyl	
1236	n-butyl	n-butyl	4-(bromomethyl)phenyl
1237	n-butyl	n-butyl	
1238	n-butyl	n-butyl	

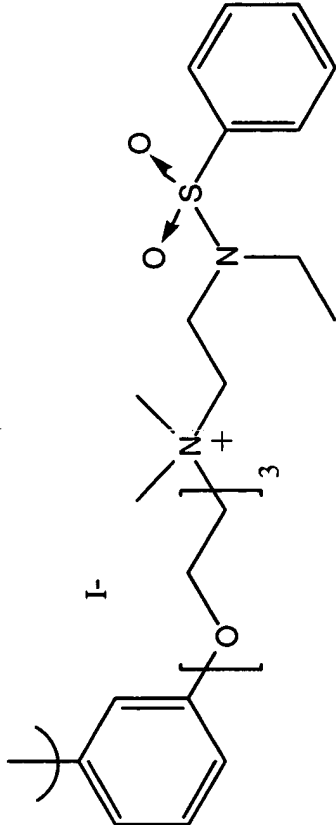
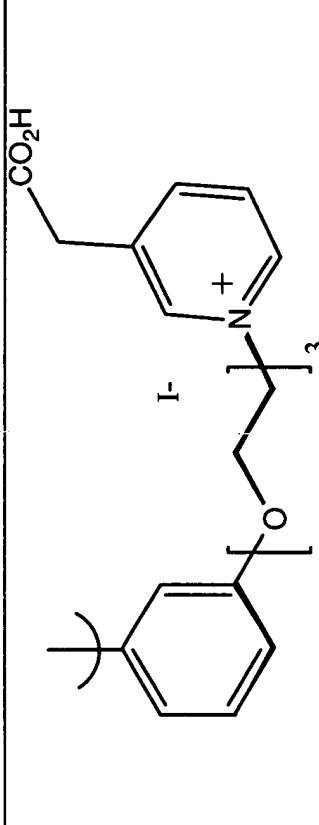
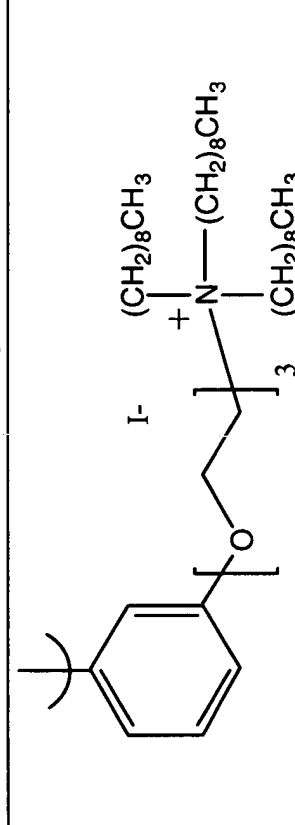
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1239	n-butyl	n-butyl	
1240	n-butyl	n-butyl	4-methoxy-3-methylphenyl
1241	n-butyl	n-butyl	3-(dimethylaminomethyl)phenyl
1242	n-butyl	n-butyl	
1243	n-butyl	n-butyl	
1244	n-butyl	n-butyl	3-methoxyphenyl

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1245	n-butyl	n-butyl	
1246	n-butyl	n-butyl	3-(bromomethyl)phenyl
1247	n-butyl	n-butyl	
1248	n-butyl	n-butyl	
1249	n-butyl	n-butyl	
1250	n-butyl	n-butyl	3-(dimethylamino)phenyl
1251	n-butyl	n-butyl	1-naphthyl

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1252	n-butyl	n-butyl	
1253	n-butyl	n-butyl	
1254	n-butyl	n-butyl	
1255	n-butyl	n-butyl	
1256	n-butyl	n-butyl	3-nitrophenyl
1257	n-butyl	n-butyl	phenyl
1258	n-butyl	n-butyl	4-fluorophenyl

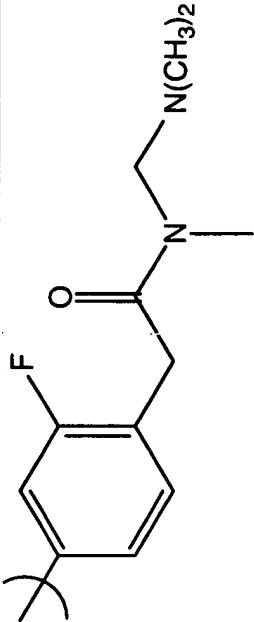
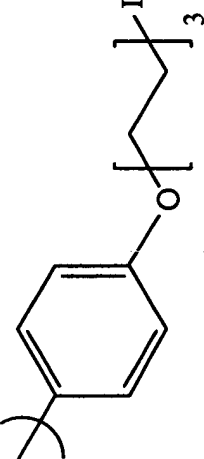
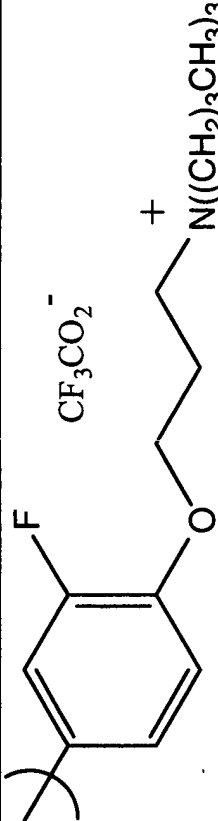
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1259	Ethyl	n-butyl	H
1260	Ethyl	n-butyl	3-hydroxyphenyl
1261	n-butyl	n-butyl	
1262	n-butyl	n-butyl	2-thiophenyl
1263	n-butyl	n-butyl	5-piperonyl
1264	n-butyl	n-butyl	4-fluorophenyl
1265	n-butyl	n-butyl	4-fluorophenyl

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1266	n-butyl	n-butyl	
1267	n-butyl	ethyl	5-piperonyl
1268	n-butyl	n-butyl	
1269	n-butyl	n-butyl	
1270	n-butyl	n-butyl	

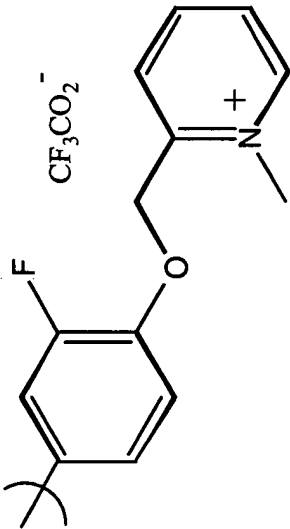
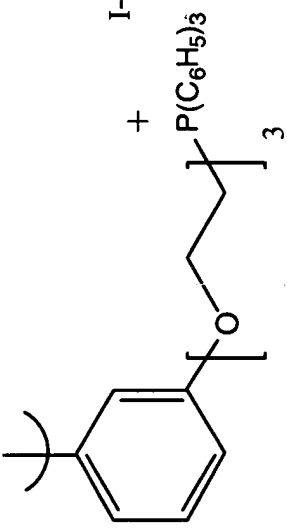
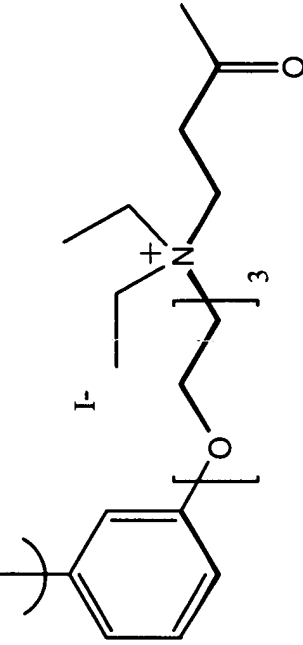
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1271	n-butyl	n-butyl	
1272	n-butyl	n-butyl	
1273	n-butyl	n-butyl	

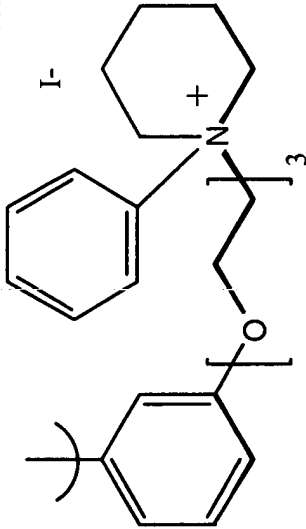
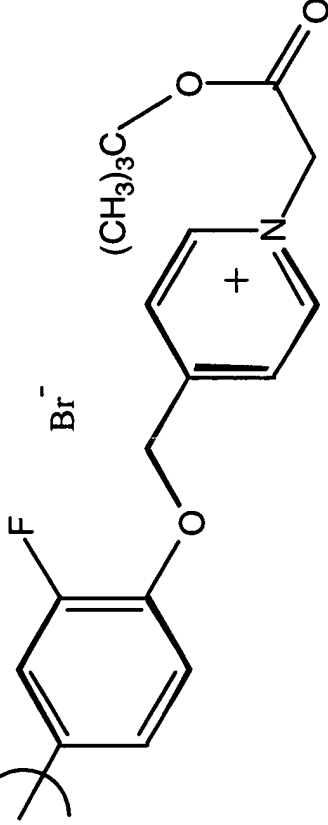
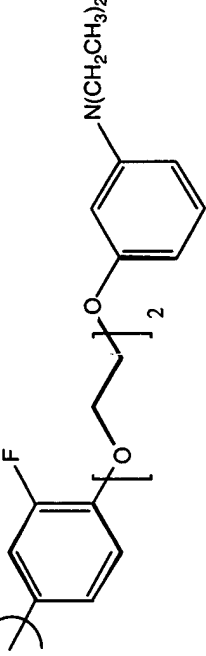
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1274	n-butyl	n-butyl	
1275	n-butyl	n-butyl	
1276	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1277	n-butyl	n-butyl	
1278	n-butyl	n-butyl	
1279	n-butyl	n-butyl	

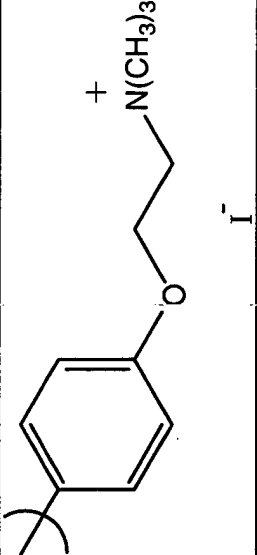
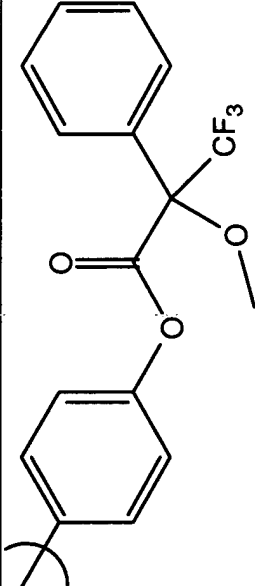
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1280	n-butyl	n-butyl	
1281	n-butyl	n-butyl	
1282	Ethyl	n-butyl	3-fluoro-4-methoxyphenyl
1283	n-butyl	n-butyl	4-hydroxymethylphenyl
1284	n-butyl	n-butyl	4-fluorophenyl
1285	n-butyl	ethyl	phenyl
1286	n-butyl	n-butyl	
1287	n-butyl	ethyl	4-hydroxyphenyl

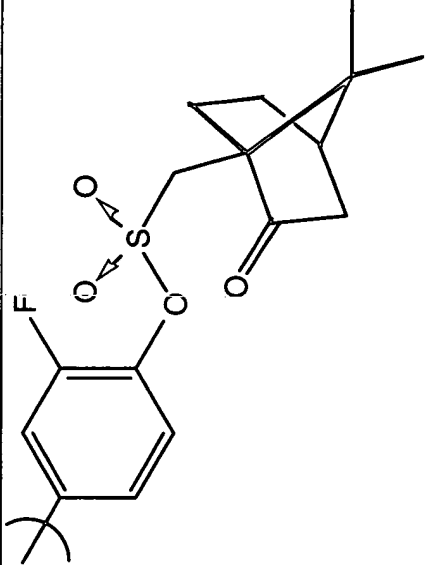
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1288	n-butyl	n-butyl	
1289	n-butyl	n-butyl	
1290	n-butyl	n-butyl	

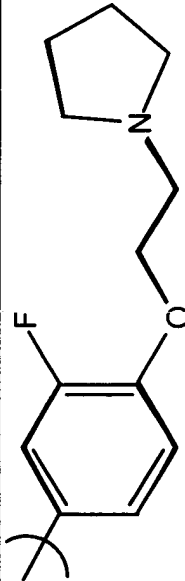
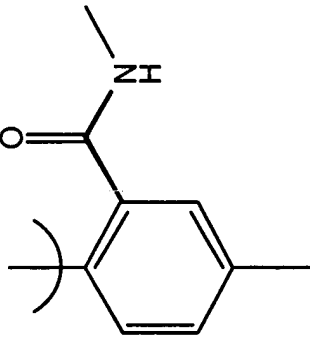
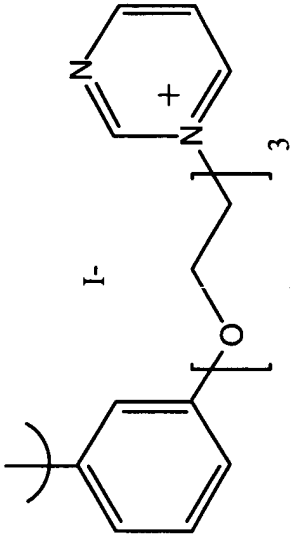
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1291	n-butyl	n-butyl	
1292	n-butyl	n-butyl	
1293	n-butyl	n-butyl	

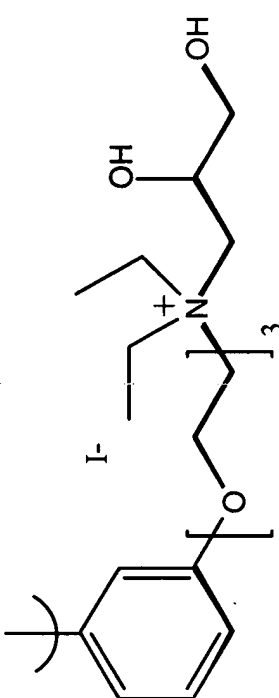
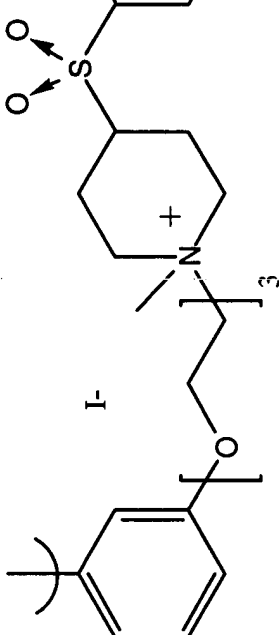
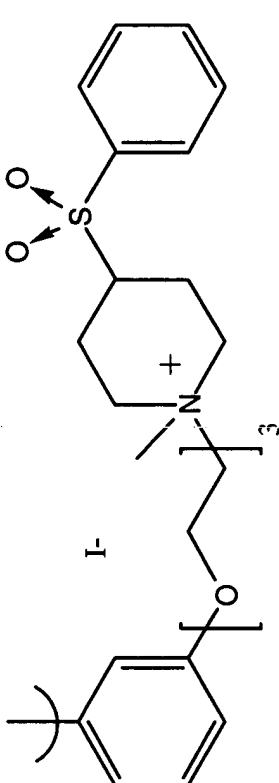
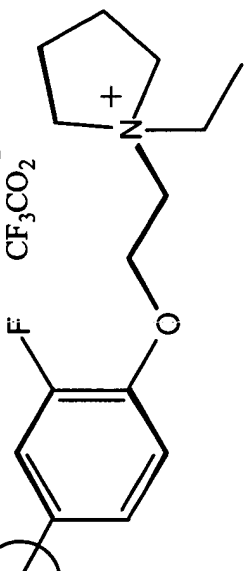
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1294	n-butyl	n-butyl	
1295	n-butyl	n-butyl	
1296	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1297	n-butyl	n-butyl	
1298	n-butyl	n-butyl	
1299	n-butyl	n-butyl	
1300	n-butyl	ethyl	H
1301	n-butyl	n-butyl	3-methoxyphenyl
1302	n-butyl	n-butyl	3-hydroxyphenyl

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1303	n-butyl	n-butyl	
1304	n-butyl	n-butyl	3-methoxyphenyl
1305	n-butyl	n-butyl	4-fluorophenyl
1306	n-butyl	n-butyl	
1307	n-butyl	n-butyl	H

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1308	Ethyl	n-butyl	
1309	n-butyl	n-butyl	4-methoxyphenyl
1310	Ethyl	n-butyl	phenyl
1311	n-butyl	ethyl	phenyl
1312	n-butyl	ethyl	phenyl
1313	n-butyl	ethyl	phenyl
1314	Ethyl	n-butyl	phenyl
1315	Ethyl	n-butyl	phenyl
1316	n-butyl	ethyl	phenyl
1317	n-butyl	ethyl	phenyl
1318	Ethyl	n-butyl	phenyl
1319	Ethyl	n-butyl	3-methoxyphenyl
1320	Ethyl	n-butyl	phenyl
1321	n-butyl	ethyl	phenyl

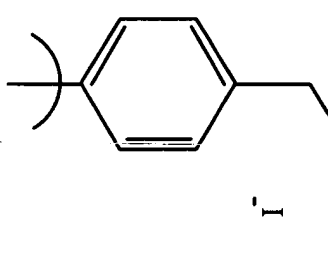
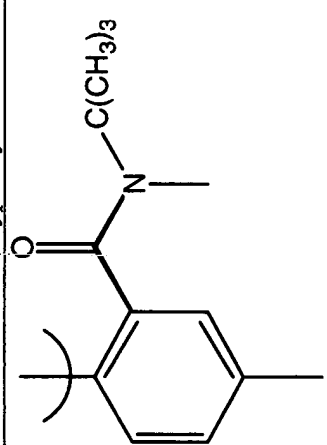
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1322	n-butyl	n-butyl	
1323	n-butyl	n-butyl	
1324	n-butyl	n-butyl	
1325	n-butyl	n-butyl	4-((diethylamino)methyl)phenyl

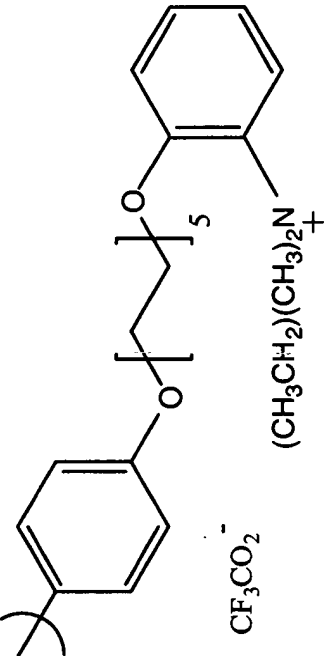
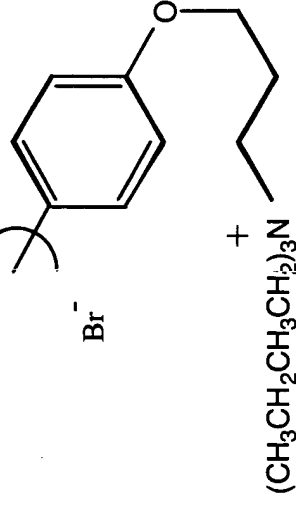
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1326	n-butyl	n-butyl	
1327	n-butyl	n-butyl	
1328	n-butyl	n-butyl	
1329	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1330	n-butyl	n-butyl	
1331	n-butyl	n-butyl	

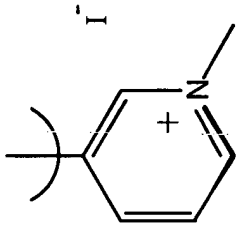
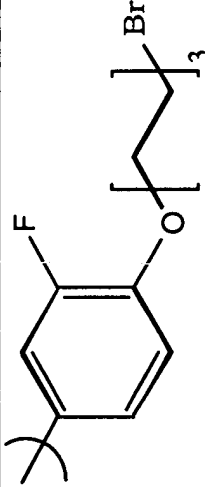
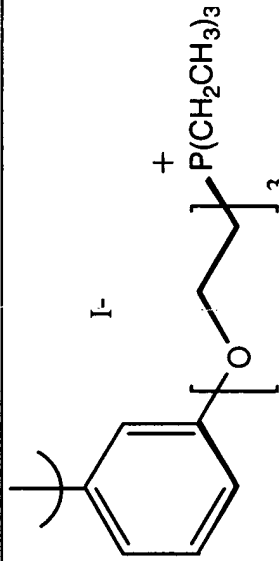
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1332	n-butyl	n-butyl	
1333	n-butyl	n-butyl	
1334	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1335	n-butyl	n-butyl	
1336	n-butyl	n-butyl	

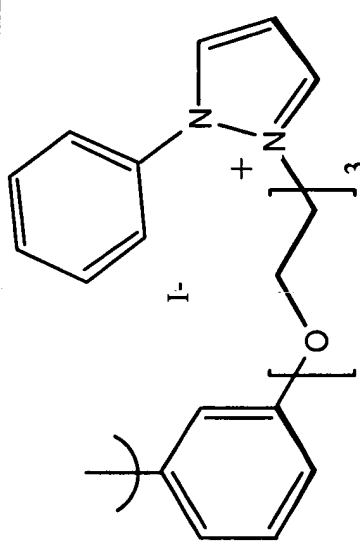
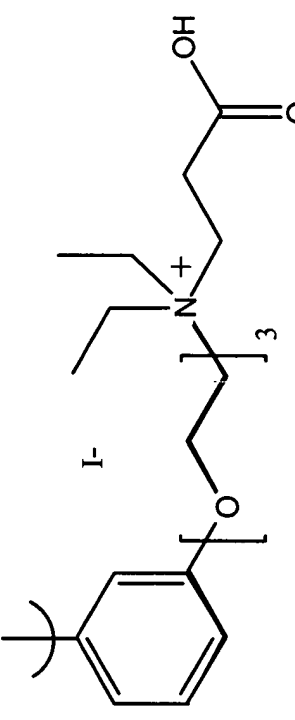
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1337	n-butyl	n-butyl	 I^- $(\text{H}_3\text{C})_3\text{N}^+$
1338	n-butyl	n-butyl	4-methoxyphenyl
1339	n-butyl	n-butyl	 I^- $(\text{H}_3\text{C})_3\text{N}^+$
1340	n-butyl	ethyl	5-piperonyl
1341	n-butyl	n-butyl	3-methoxyphenyl
1342	n-butyl	n-butyl	5-piperonyl
1343	Ethyl	n-butyl	phenyl
1344	n-butyl	n-butyl	3-fluoro-4-methoxyphenyl

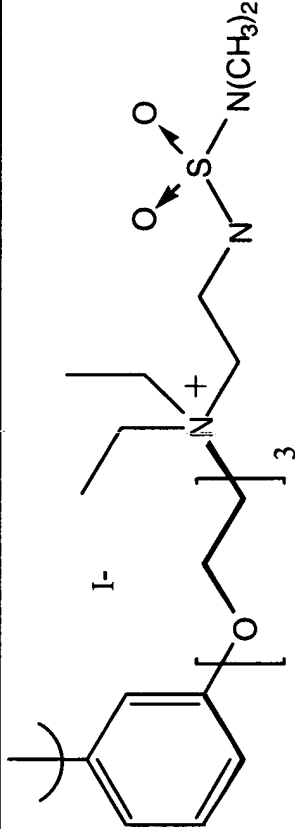
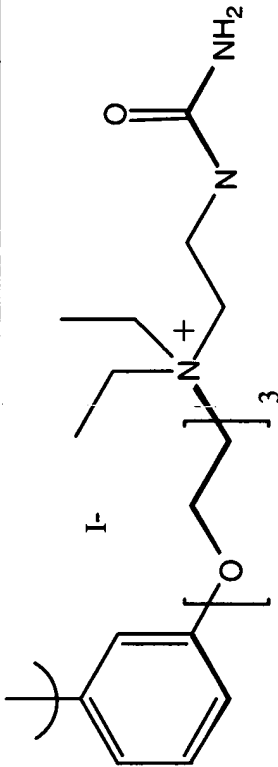
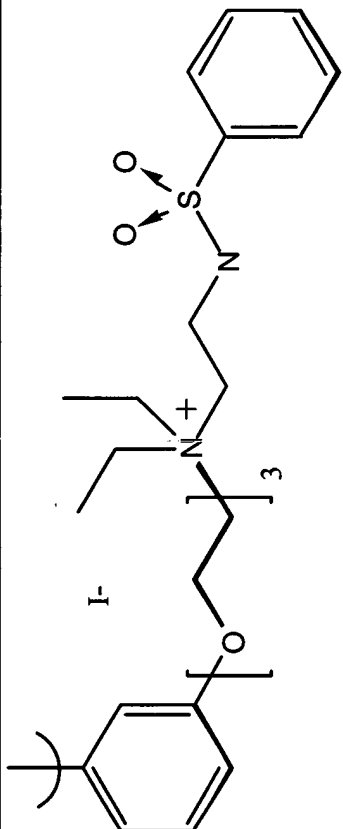
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1345	Ethyl	n-butyl	phenyl
1346	Ethyl	n-butyl	phenyl
1347	n-butyl	n-butyl	3-fluoro-4-methoxyphenyl
1348	isobutyl	isobutyl	phenyl
1349	Ethyl	n-butyl	phenyl
1350	n-butyl	n-butyl	3-fluoro-4-methoxyphenyl
1351	n-butyl	n-butyl	
1352	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1353	n-butyl	n-butyl	
1354	n-butyl	n-butyl	
1355	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1356	n-butyl	n-butyl	
1357	n-butyl	n-butyl	
1358	n-butyl	n-butyl	

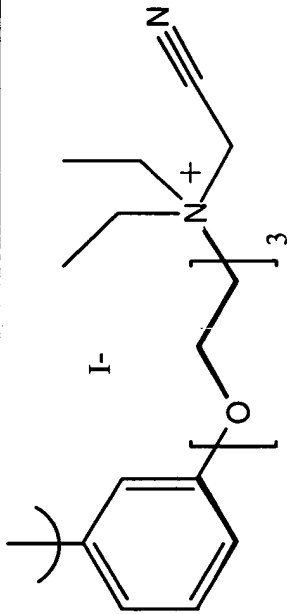
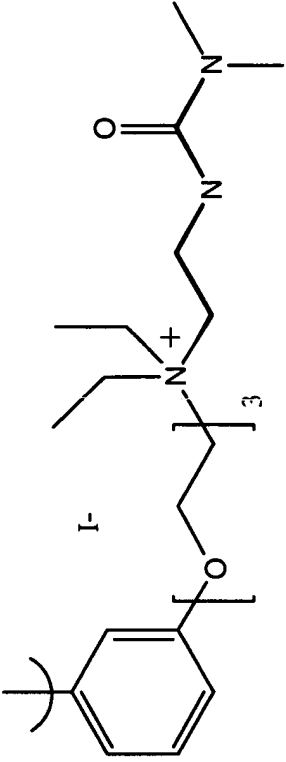
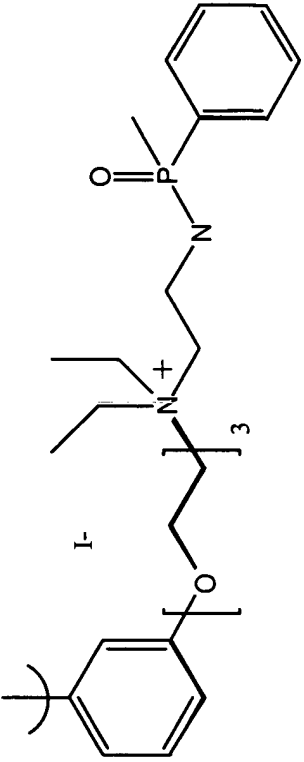
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1359	n-butyl	n-butyl	
1360	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1361	n-butyl	n-butyl	
1362	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1363	n-butyl	n-butyl	
1364	n-butyl	n-butyl	
1365	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1366	n-butyl	n-butyl	
1367	n-butyl	n-butyl	
1368	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1369	n-butyl	n-butyl	
1370	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1371	n-butyl	n-butyl	
1372	n-butyl	n-butyl	
1373	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1374	n-butyl	n-butyl	
1375	n-butyl	n-butyl	
1376	n-butyl	n-butyl	

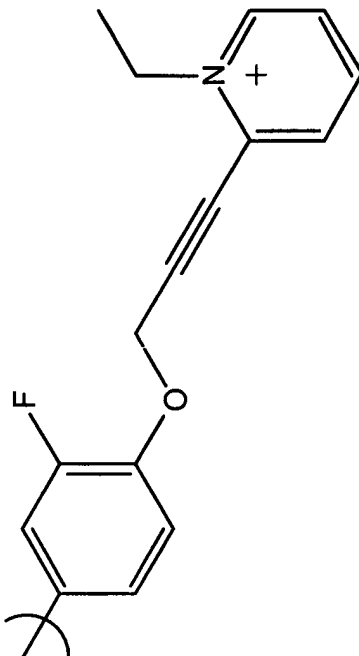
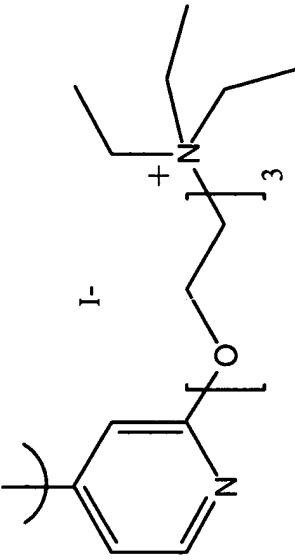
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1377	n-butyl	n-butyl	
1378	n-butyl	n-butyl	
1379	n-butyl	n-butyl	

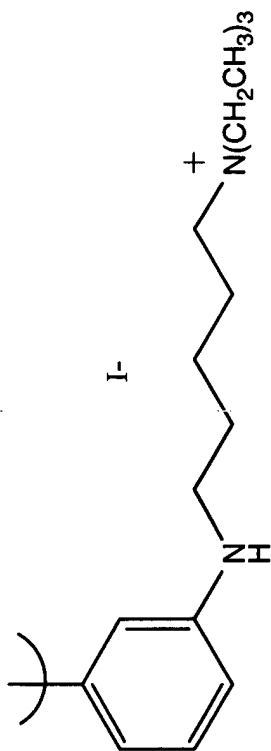
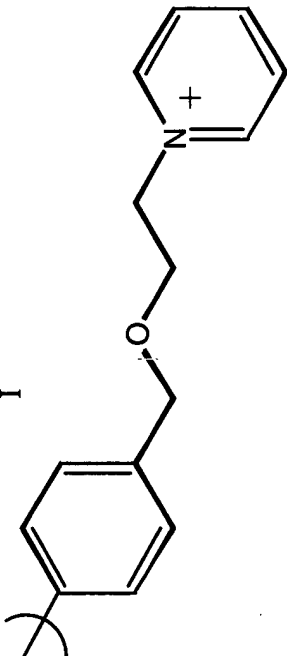
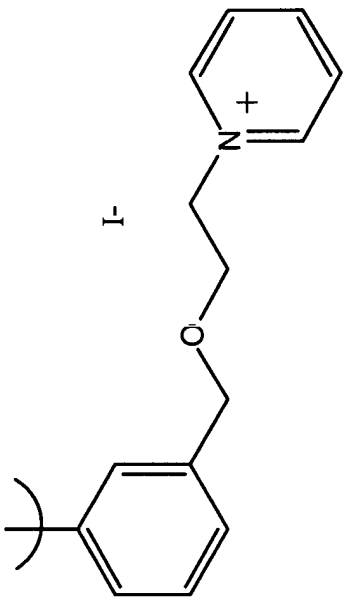
Compound Number	R ^{2A}	R ^{2B}	R ^S
1380	n-butyl	n-butyl	
1381	n-butyl	n-butyl	
1382	n-butyl	n-butyl	

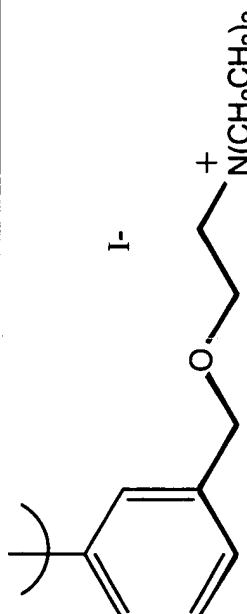
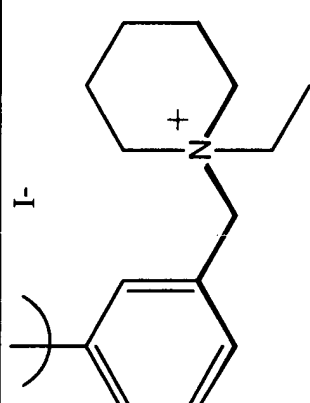
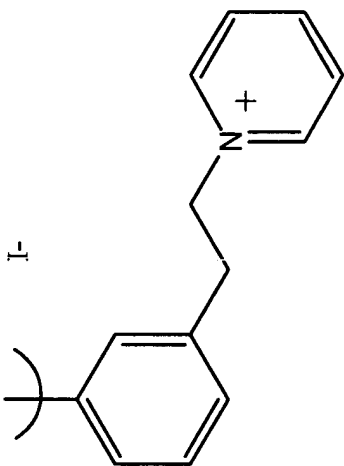
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1383	n-butyl	n-butyl	
1384	n-butyl	n-butyl	
1385	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1386	n-butyl	n-butyl	
1387	n-butyl	n-butyl	
1388	n-butyl	n-butyl	

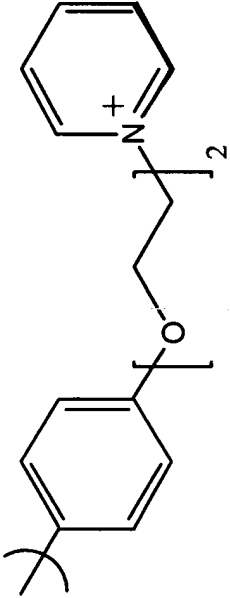
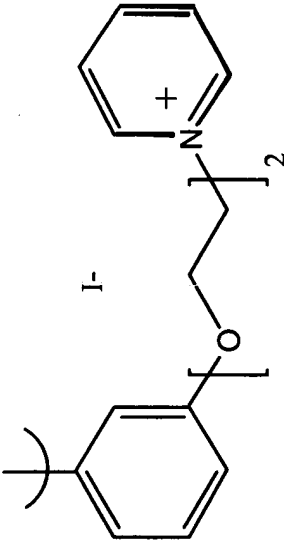
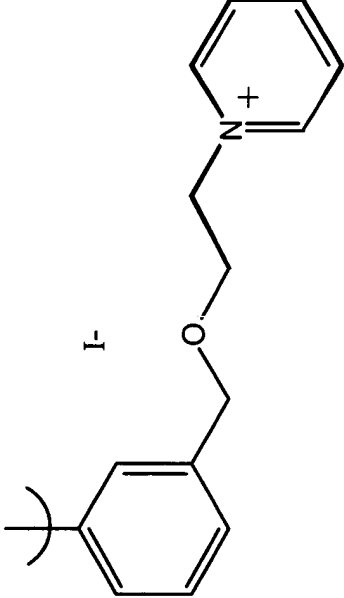
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1389	n-butyl	n-butyl	
1390	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1391	n-butyl	n-butyl	
1392	n-butyl	n-butyl	

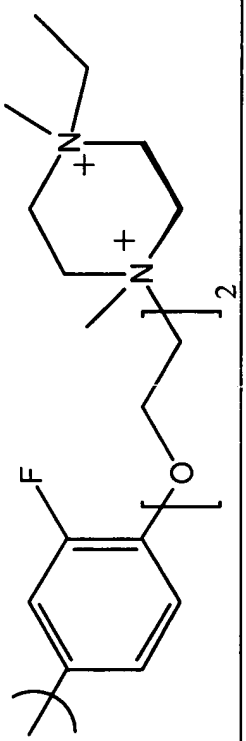
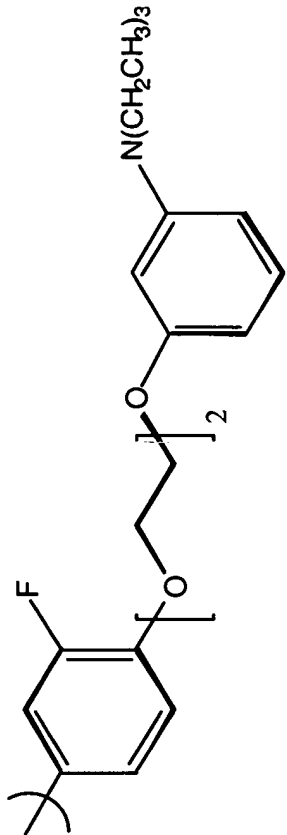
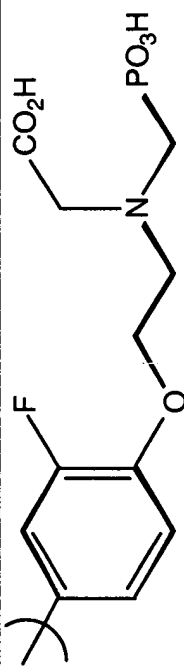
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1393	n-butyl	n-butyl	
1394	n-butyl	n-butyl	
1395	n-butyl	n-butyl	

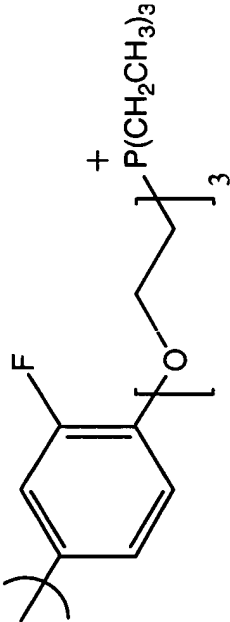
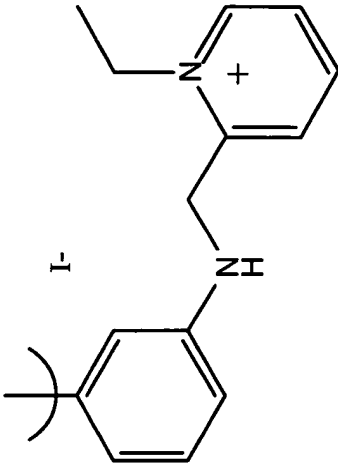
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1396	n-butyl	n-butyl	
1397	n-butyl	n-butyl	
1398	n-butyl	n-butyl	

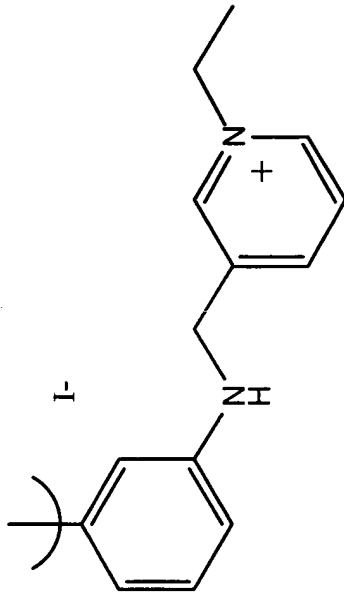
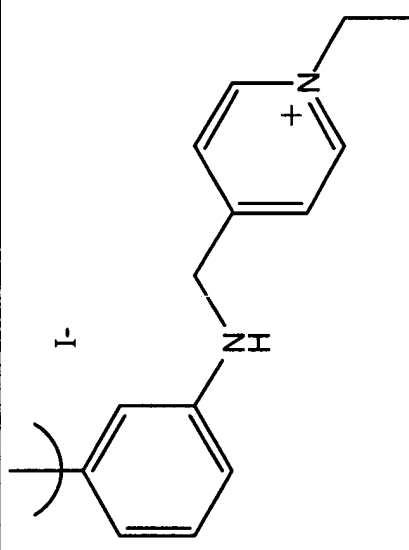
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1399	n-butyl	n-butyl	
1400	n-butyl	n-butyl	
1401	n-butyl	n-butyl	

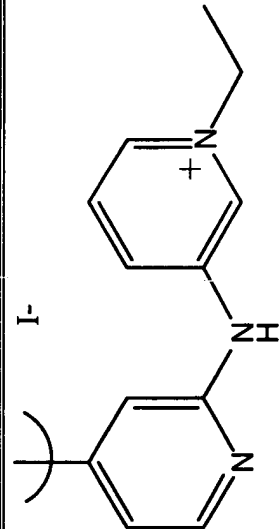
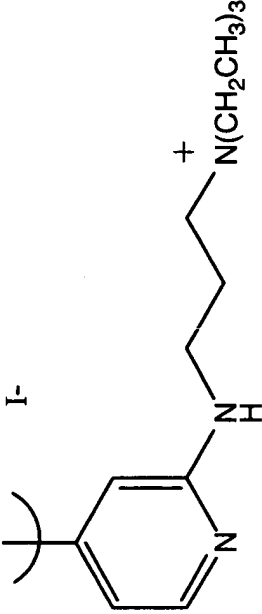
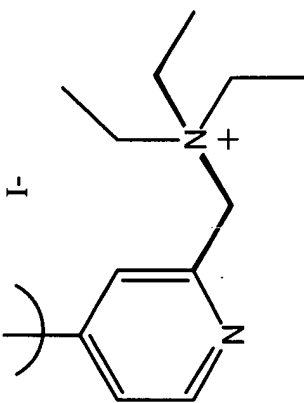
Compound Number	R ^{2A}	R ^{2B}	R ^S
1402	n-butyl	n-butyl	
1403	n-butyl	n-butyl	
1404	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1405	n-butyl	n-butyl	
1406	n-butyl	n-butyl	
1407	n-butyl	n-butyl	

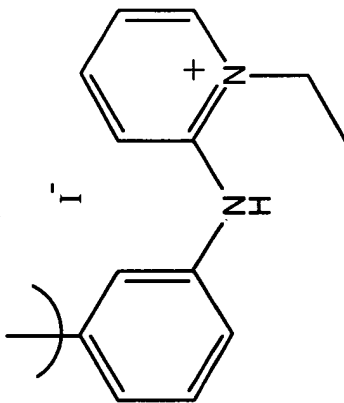
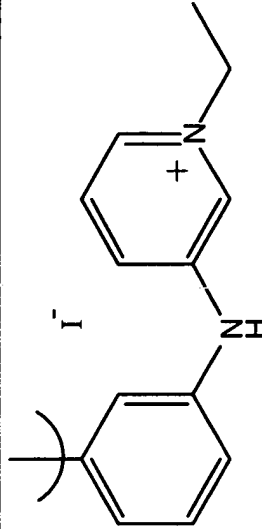
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1408	n-butyl	n-butyl	
1409	n-butyl	n-butyl	
1410	n-butyl	n-butyl	

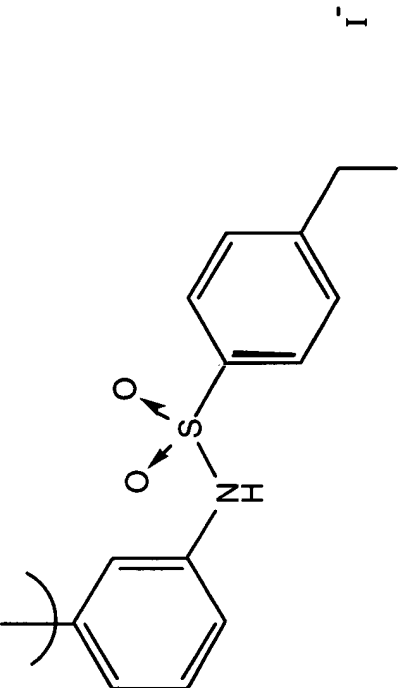
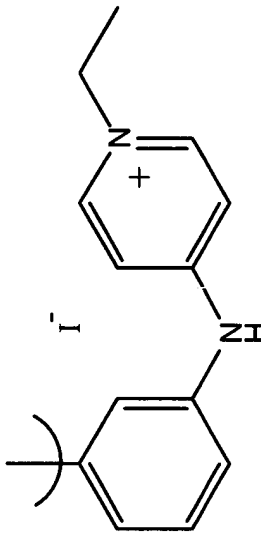
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1411	n-butyl	n-butyl	
1412	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1413	n-butyl	n-butyl	
1414	n-butyl	n-butyl	

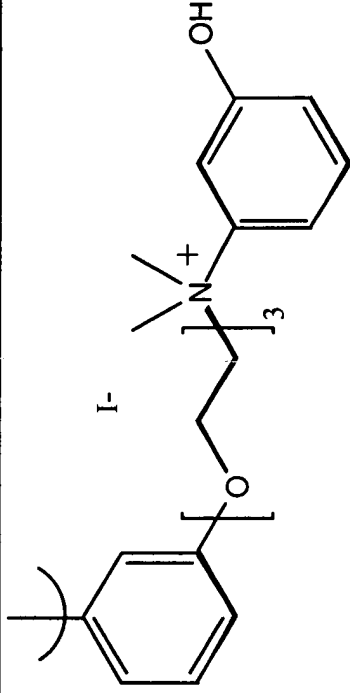
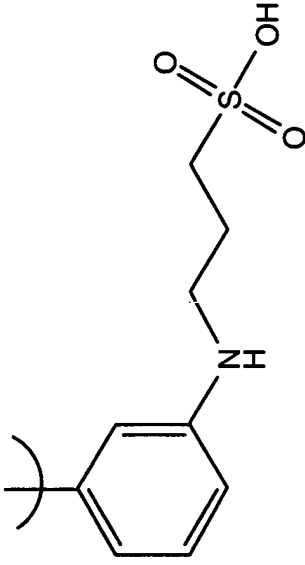
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1415	n-butyl	n-butyl	
1416	n-butyl	n-butyl	
1417	n-butyl	n-butyl	

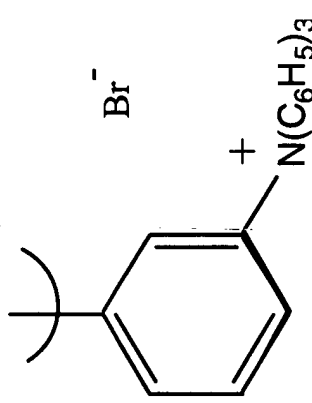
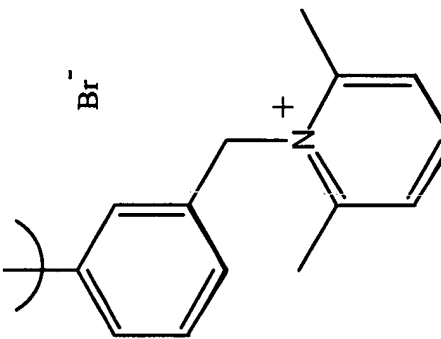
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1418	n-butyl	n-butyl	
1419	n-butyl	n-butyl	

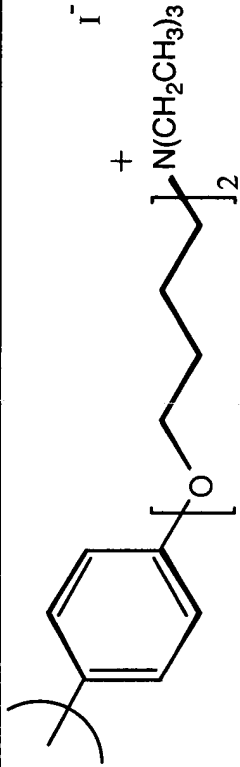
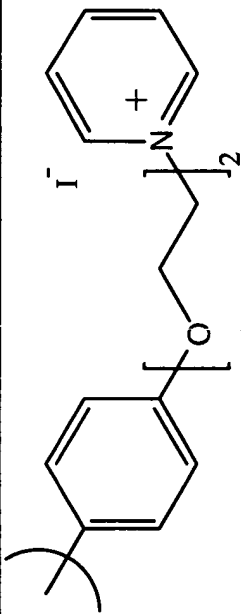
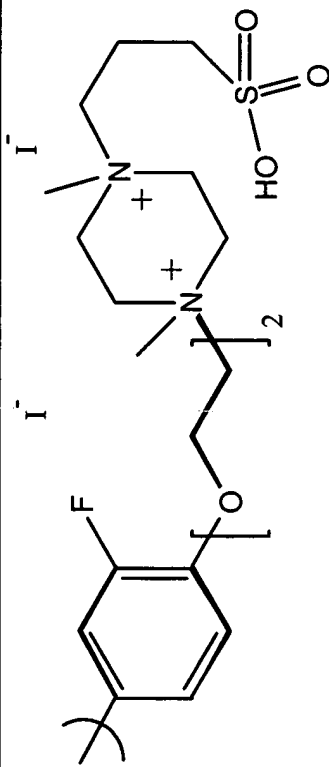
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1420	n-butyl	n-butyl	
1421	n-butyl	n-butyl	

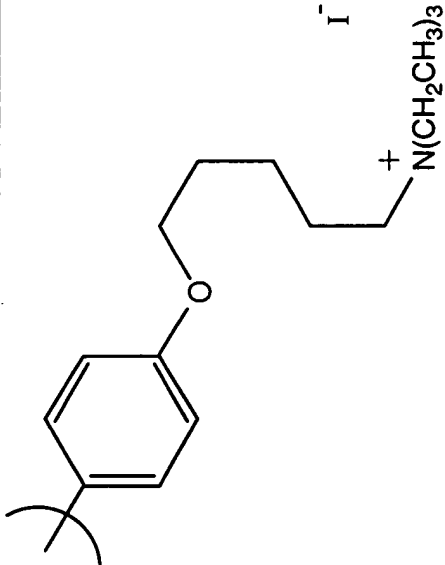
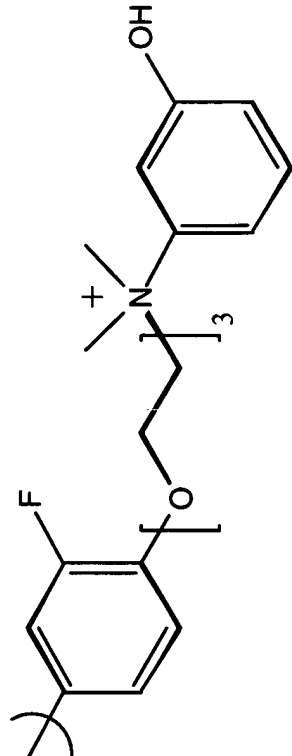
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1422	n-butyl	n-butyl	 I^- $+ \text{N}(\text{CH}_2\text{CH}_3)_3$
1423	n-butyl	n-butyl	 I^-

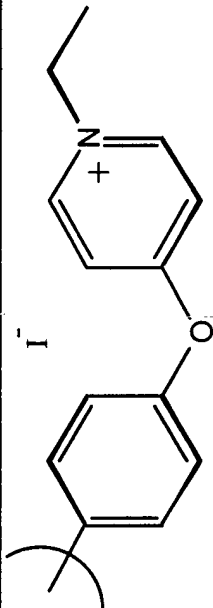
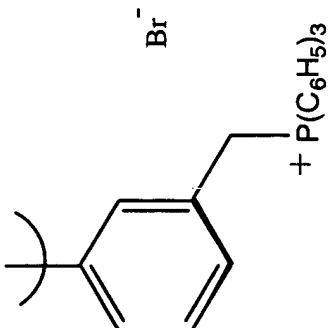
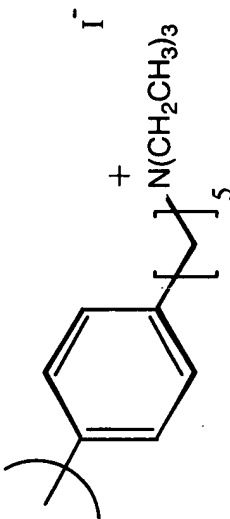
Compound Number	R ^{2A}	R ^{2B}	R ^S
1424	n-butyl	n-butyl	
1425	n-butyl	n-butyl	
1426	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1427	n-butyl	n-butyl	
1428	n-butyl	n-butyl	

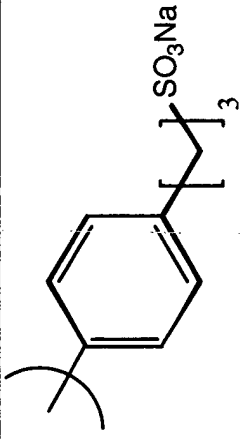
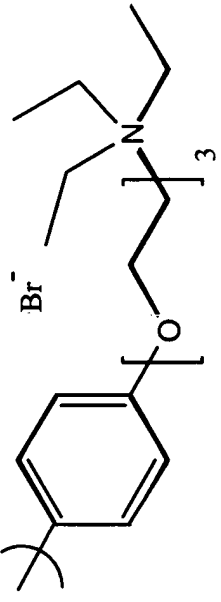
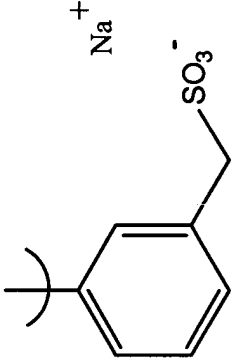
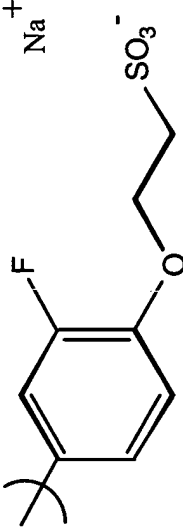
Compound Number	R ^{2A}	R ^{2B}	R ⁵
1429	n-butyl	n-butyl	
1430	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1431	n-butyl	n-butyl	
1432	n-butyl	n-butyl	
1433	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1434	n-butyl	n-butyl	
1435	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1436	n-butyl	n-butyl	
1437	n-butyl	n-butyl	
1438	n-butyl	n-butyl	

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1439	n-butyl	n-butyl	<p>Chemical structure of compound 1439: A polymer chain with a phenyl ring and a quaternary ammonium group, with an iodide counterion.</p>
1440	n-butyl	n-butyl	<p>Chemical structure of compound 1440: A polymer chain with a fluorophenyl ring and a quaternary ammonium group, with an iodide counterion.</p>
1441	n-butyl	n-butyl	<p>Chemical structure of compound 1441: A polymer chain with a fluorophenyl ring and a quaternary ammonium group, with an iodide counterion.</p>

Compound Number	R ^{2A}	R ^{2B}	R ⁵
1445	n-butyl	n-butyl	
1446	n-butyl	n-butyl	
1447	n-butyl	n-butyl	
1448	n-butyl	n-butyl	

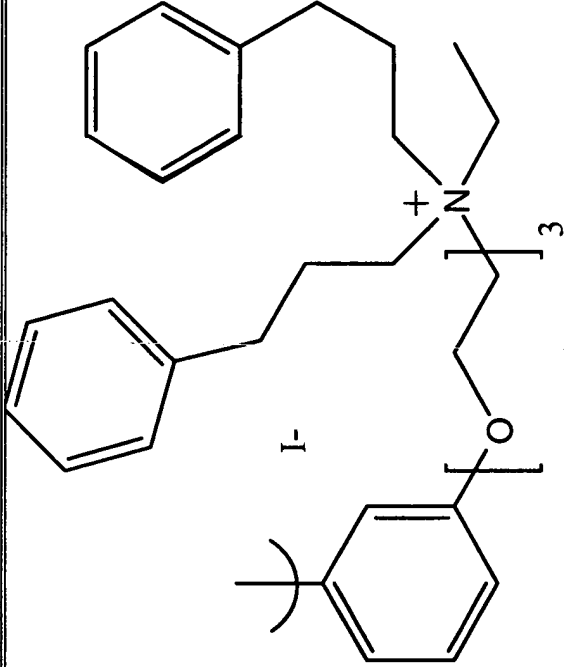
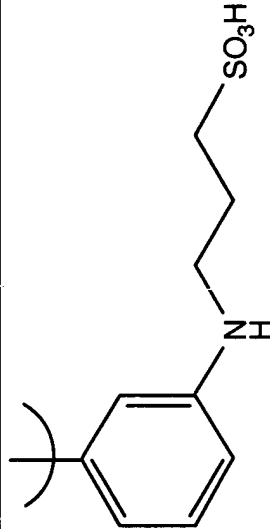
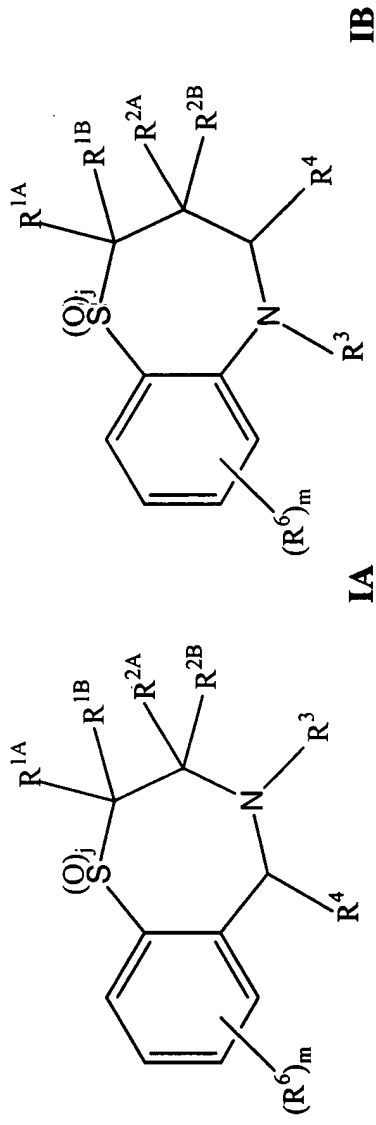
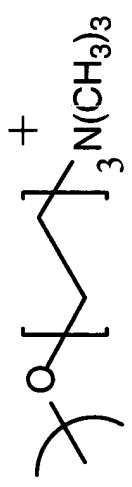
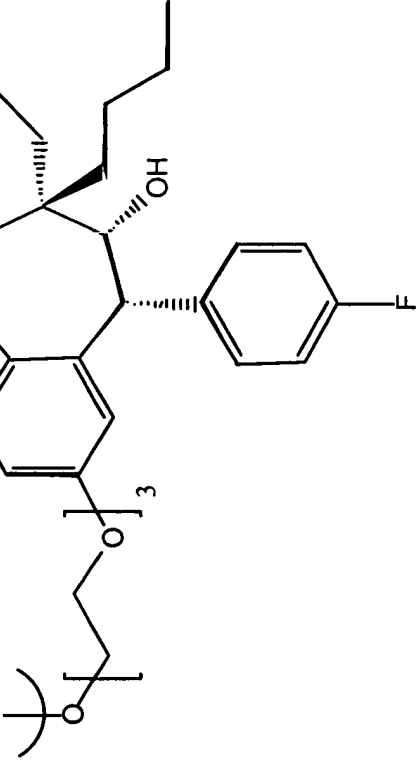
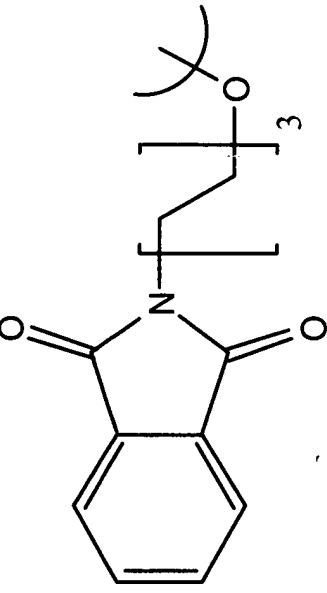
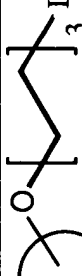
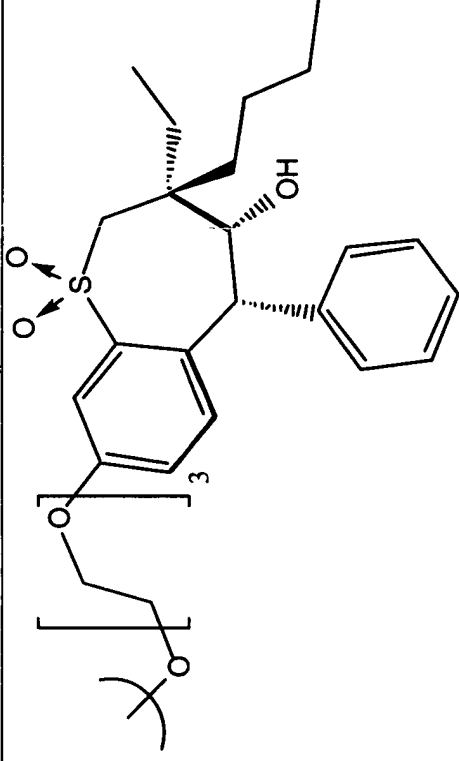
Compound Number	R ^{2A}	R ^{2B}	R ^S
1449	n-butyl	n-butyl	
1450	n-butyl	n-butyl	phenyl
1451	n-butyl	n-butyl	

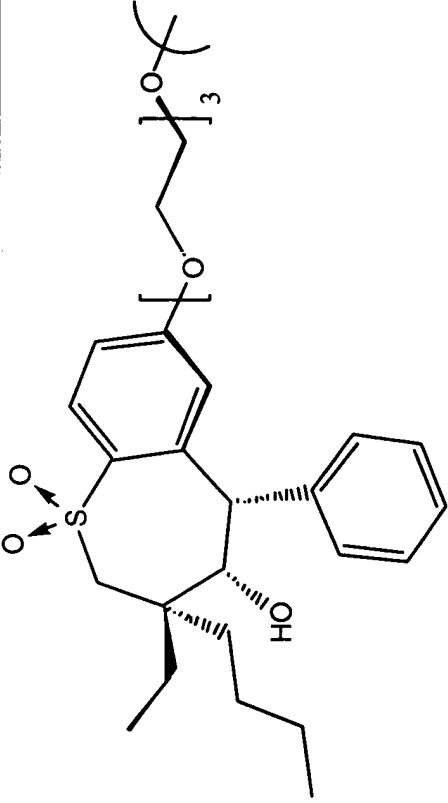
Table 10 (continuation of Table 9 substituents)

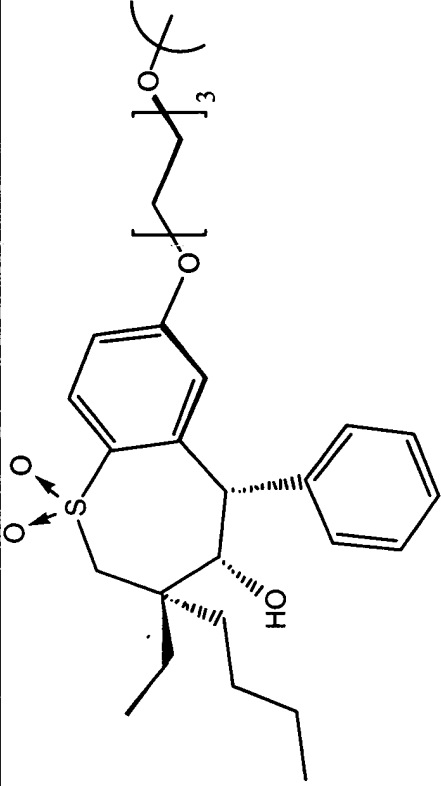


Compound Number	(R ⁶) _m
114	7-amino
115	7-(O-benzylcarbamato)
116	7-(O-benzylcarbamato)
117	7-(O-benzylcarbamato)
118	7-(O-benzylcarbamato)
119	7-(O-tert-butylcarbamato)
120	7-(O-benzylcarbamato)
121	7-amino
122	7-amino
123	7-hexylamino
124	7-(hexylamino)
125	<div style="text-align: center;">  <p>at the 8-position</p> </div>
126	7-(O-benzylcarbamato)
127	7-amino
128	7-(O-benzylcarbamato)
129	7-amino

Compound Number	$(R^6)_m$
131	 <p>at the 7-position</p>
132	 <p>at the 8-position</p>

Compound Number	(R ⁶) _m
133	8-(hexyloxy)
134	
135	
136	at the 8-position 8-hydroxy

Compound Number	$(R^6)_m$
137	
138	<p>at the 7-position 8-acetoxy</p>

Compound Number	(R ⁶) _m
139	 <p>at the 7-position</p>
140	
141	
142	7-methylmercapto
143	7-methylmercapto
144	7-(N-azetidiny)
262	7-methoxy
263	7-methoxy
264	7-methoxy
265	7-methoxy
266	7-hydroxy
267	7-methoxy
268	7-methoxy
269	7-methoxy

Compound Number	(R ⁶) _m
270	7-hydroxy
271	7-bromo
272	7-bromo
273	7-fluoro
274	7-fluoro
275	7-fluoro
276	7-fluoro
277	7-methoxy
278	7-methoxy
279	7-methoxy
280	7-methoxy
281	7-methylmercapto
282	7-methyl
283	7-methyl
284	7-(4'-morpholino)
286	7-(O-benzylcarbamato)
287	7-amino
288	7-amino
289	7-amino
290	7-amino
291	7-(O-benzylcarbamato)
292	7-amino
293	7-benzylamino
294	7-dimethylamino
295	7-amino
296	7-amino

Compound Number	(R) _m
1000	7-dimethylamino
1001	7-dimethylamino
1002	7-dimethylamino
1003	7-dimethylamino
1004	7-dimethylamino
1005	7-dimethylamino
1006	7-dimethylamino
1007	7-dimethylamino
1008	7-dimethylamino
1009	7-dimethylamino
1010	7-dimethylamino
1011	7-dimethylamino
1012	7-dimethylamino; 9-methoxy
1013	7-dimethylamino
1014	7-dimethylamino; 9-methoxy
1015	7-dimethylamino
1016	7-dimethylamino
1017	7-dimethylamino
1018	7-dimethylamino
1019	7-dimethylamino
1020	7-dimethylamino
1021	7-dimethylamino
1022	7-dimethylamino
1023	7-dimethylamino
1024	7-dimethylamino
1025	7-dimethylamino

Compound Number	(R ⁶) _m
1026	7-dimethylamino
1027	7-dimethylamino
1028	7-dimethylamino
1029	7-dimethylamino
1030	7-dimethylamino
1031	7-dimethylamino
1032	7-dimethylamino
1033	7-dimethylamino
1034	7-dimethylamino
1035	7-dimethylamino
1036	7-dimethylamino
1037	7-dimethylamino
1038	7-dimethylamino
1039	7-dimethylamino
1040	7-dimethylamino
1041	7-dimethylamino
1042	7-dimethylamino
1043	7-dimethylamino
1044	7-dimethylamino
1045	7-dimethylamino
1046	7-dimethylamino
1047	7-dimethylamino
1048	7-dimethylamino
1049	7-dimethylamino
1050	7-dimethylamino
1051	7-dimethylamino

Compound Number	(R) ⁶ _m
1052	7-dimethylamino
1053	7-dimethylamino
1054	7-dimethylamino
1055	7-dimethylamino
1056	7-dimethylamino
1057	7-dimethylamino
1058	7-dimethylamino
1059	7-dimethylamino
1060	7-methylamino
1061	7-methylamino
1062	7-methylamino
1063	7-methylamino
1064	7-methylamino
1065	7-dimethylamino
1066	7-dimethylamino
1067	9-dimethylamino
1068	7-dimethylamino
1069	7-dimethylamino; 9-dimethylamino
1070	7-dimethylamino
1071	7-dimethylamino
1072	7-dimethylamino
1073	7-dimethylamino
1074	7-dimethylamino
1075	7-dimethylamino; 9-dimethylamino
1076	7-dimethylamino

Compound Number	(R) _m
1077	7-dimethylamino
1078	7-dimethylamino
1079	7-dimethylamino
1080	7-dimethylamino
1081	7-dimethylamino
1082	7-dimethylamino
1083	7-dimethylamino
1084	7-dimethylamino
1085	7-dimethylamino
1086	7-dimethylamino
1087	7-dimethylamino
1088	7-dimethylamino
1089	7-dimethylamino
1090	7-dimethylamino
1091	7-dimethylamino
1092	7-dimethylamino
1093	7-dimethylamino
1094	7-dimethylamino
1095	7-dimethylamino
1096	7-dimethylamino
1097	7-dimethylamino
1098	7-dimethylamino
1099	7-dimethylamino
1100	7-dimethylamino
1101	7-dimethylamino
1102	7-dimethylamino

Compound Number	(R) _m
1103	7-dimethylamino
1104	7-dimethylamino
1105	7-dimethylamino
1106	7-dimethylamino
1107	7-dimethylamino
1108	7-dimethylamino
1109	7-dimethylamino
1110	7-dimethylamino
1111	7-dimethylamino
1112	7-dimethylamino
1113	7-dimethylamino
1114	7-methylamino
1115	7-dimethylamino
1116	7-dimethylamino
1117	7-dimethylamino
1118	7-dimethylamino
1119	7-dimethylamino
1120	7-dimethylamino
1121	7-dimethylamino
1122	7-dimethylamino
1123	7-dimethylamino
1124	7-dimethylamino
1125	7-dimethylamino
1126	7-dimethylamino
1127	7-dimethylamino
1128	7-dimethylamino

Compound Number	(R') _m
1129	9-dimethylamino
1130	7-dimethylamino
1131	7-dimethylamino
1132	7-dimethylamino
1133	7-dimethylamino
1134	7-dimethylamino
1135	7-dimethylamino
1136	7-dimethylamino
1137	9-(2',2'-dimethylhydrazino)
1138	7-dimethylamino
1139	7-dimethylamino
1140	7-(2',2'-dimethylhydrazino)
1141	7-ethylmethylamino
1142	7-dimethylamino
1143	7-dimethylamino
1144	7-dimethylamino
1145	9-dimethylamino
1146	7-dimethylamino
1147	7-diethylamino
1148	7-dimethylsulfonium, fluoride salt
1149	7-ethylamino
1150	7-ethylmethylamino
1151	7-dimethylamino
1152	7-(ethoxymethyl) methylamino
1153	7-methylamino
1154	9-methoxy

Compound Number	(R ⁶) _m
1155	7-methyl
1156	7-methylmercapto
1157	7-fluoro; 9-dimethylamino
1158	7-methoxy
1159	7-dimethylamino
1160	7-diethylamino
1161	7-dimethylamino
1162	7-dimethylamino
1163	7-methoxy
1164	7-methoxy
1165	7-trimethylammonium iodide
1166	7-trimethylammonium iodide
1167	7-dimethylamino
1168	7-trimethylammonium iodide
1169	8-dimethylamino
1170	7-ethylpropylamino
1171	7-dimethylamino
1172	7-methoxy
1173	7-ethylpropylamino
1174	7-phenyl
1175	7-methylsulfonyl
1176	9-fluoro
1177	7-butylmethylamino
1178	7-dimethylamino
1179	8-methoxy

Compound Number	(R ⁶) _m
1180	7-trimethylammonium iodide
1181	7-butylmethylamino
1182	7-methoxy
1183	7-fluoro
1184	7-fluoro; 9-fluoro
1185	7-fluoro
1186	7-fluoro; 9-fluoro
1187	7-methyl
1188	7-trimethylammonium iodide
1189	7-trimethylammonium iodide
1190	7-bromo
1191	7-hydroxy
1192	7-hydroxy
1193	7-dimethylamino
1194	7-dimethylamino
1195	7-(4'-methylpiperazin-1-yl)
1196	7-methoxy
1197	7-(N-methylformamido)
1198	7-methoxy
1199	7-dimethylamino
1200	7-dimethylamino
1201	7-methyl
1202	7-methoxy
1203	7-(4'-tert-butylphenyl)
1204	7-methoxy
1205	7-dimethylamino

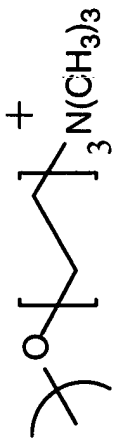
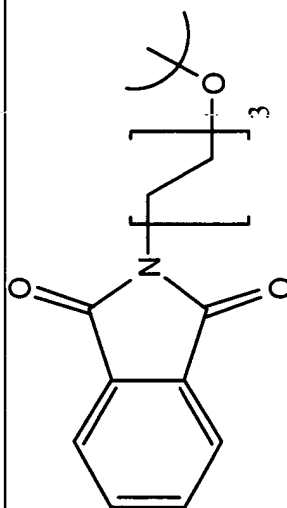
Compound Number	(R ⁶) _m
1206	7-dimethylamino
1207	7-dimethylamino
1208	7-dimethylamino
1209	7-dimethylphenyl
1210	7-dimethylamino
1211	7-dimethylamino
1212	9-(4'-morpholino)
1213	7-dimethylamino
1214	7-(N-methylformamido)
1215	9-methylmercapto
1216	7-bromo
1217	7-dimethylamino
1218	9-methylsulfonyl
1219	7-dimethylamino
1220	7-isopropylamino
1221	7-dimethylamino
1222	7-ethylamino
1223	8-bromo; 7-methylamino
1224	7-fluoro
1225	7-dimethylamino
1226	7-bromo
1227	7-(tert-butylamino)
1228	8-bromo; 7-dimethylamino
1229	7-dimethylamino
1230	9-dimethylamino;

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Compound Number	(R) ⁶ _m
	7-fluoro
1231	7-dimethylamino
1232	9-dimethylamino
1233	7-dimethylamino
1234	7-dimethylamino
1235	7-dimethylamino
1236	7-dimethylamino
1237	7-dimethylamino
1238	7-dimethylamino
1239	7-dimethylamino
1240	7-dimethylamino
1241	7-dimethylamino
1242	7-dimethylamino
1243	7-dimethylamino
1244	7-(1'-methylhydrazido)
1245	7-dimethylamino
1246	7-dimethylamino
1247	7-dimethylamino
1248	7-dimethylamino
1249	7-dimethylamino
1250	7-dimethylamino
1251	7-dimethylamino
1252	7-dimethylamino
1253	7-dimethylamino
1254	7-dimethylamino
1255	7-dimethylamino

Compound Number	(R) _m
1256	7-dimethylamino
1257	8-bromo; 7-dimethylamino
1258	9-(tert-butylamino)
1259	7-dimethylamino
1260	7-dimethylamino
1261	7-dimethylamino
1262	7-dimethylamino
1263	7-bromo
1264	7-isopropylamino
1265	9-isopropylamino
1266	7-dimethylamino
1267	7-carboxy, methyl ester
1268	7-dimethylamino
1269	7-dimethylamino
1270	7-dimethylamino
1271	7-dimethylamino
1272	7-dimethylamino
1273	7-dimethylamino
1274	7-dimethylamino
1275	7-dimethylamino
1276	7-dimethylamino
1277	7-dimethylamino
1278	7-dimethylamino
1279	7-dimethylamino
1280	7-dimethylamino
1281	7-dimethylamino

Compound Number	(R ⁶) _m
1282	7-trimethylammonium iodide
1283	7-dimethylamino
1284	9-ethylamino
1285	7-dimethylamino
1286	7-dimethylamino
1287	7-dimethylamino
1288	7-dimethylamino
1289	7-dimethylamino
1290	7-dimethylamino
1291	7-dimethylamino
1292	7-dimethylamino
1293	7-dimethylamino
1294	7-dimethylamino
1295	7-dimethylamino
1296	7-dimethylamino
1297	7-dimethylamino
1298	7-dimethylamino
1299	7-dimethylamino
1300	7-dimethylamino
1301	7-trimethylammonium iodide
1302	9-hydroxy
1303	7-dimethylamino
1304	7-tert-butylamino
1305	9-methylamino
1306	7-dimethylamino
1307	9-(4'-morpholino)

Compound Number	(R ⁶) _m
1308	7-dimethylamino
1309	9-fluoro
1310	7-amino
1311	7-(hydroxylamino)
1312	8-hexyloxy
1313	8-ethoxy
1314	7-(hydroxylamino)
1315	7-(hexyloxy)
1316	8-hydroxy
1317	I ⁻
	
1318	at the 8-position
1319	7-dimethylamino
1320	7-fluoro
1321	7-amino
	

Compound Number	(R ⁶) _m
	at the 8-position
1322	7-dimethylamino
1323	7-dimethylamino
1324	7-dimethylamino
1325	7-dimethylamino
1326	7-dimethylamino
1327	7-dimethylamino
1328	7-dimethylamino
1329	7-dimethylamino
1330	7-dimethylamino
1331	7-dimethylamino
1332	7-dimethylamino
1333	7-dimethylamino
1334	7-dimethylamino
1335	7-dimethylamino
1336	7-dimethylamino
1337	7-dimethylamino
1338	7-(4'-methylpiperazinyl)
1339	7-dimethylamino
1340	7-methyl
1341	7-dimethylamino
1342	7-(4'-fluorophenyl)
1343	7-amino
1344	7-dimethylamino
1345	7-trimethylammonium iodide

Compound Number	(R ⁶) _m
1346	 <p>at the 8-position</p>
1347	7-dimethylamino
1348	7-dimethylamino
1349	7-dimethylamino
1350	7-trimethylammonium iodide
1351	7-dimethylamino
1352	7-dimethylamino
1353	7-dimethylamino
1354	7-dimethylamino
1355	7-dimethylamino
1356	7-dimethylamino
1357	7-dimethylamino
1358	7-dimethylamino
1359	7-dimethylamino
1360	7-dimethylamino
1361	7-dimethylamino
1362	7-dimethylamino
1363	7-dimethylamino
1364	7-dimethylamino
1365	7-dimethylamino
1366	7-dimethylamino
1367	7-dimethylamino
1368	7-dimethylamino
1369	7-dimethylamino

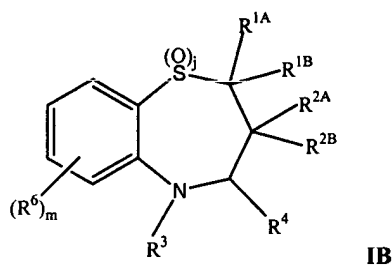
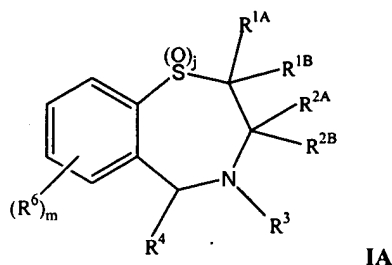
Compound Number	(R') _m
1370	7-dimethylamino
1371	7-dimethylamino
1372	7-dimethylamino
1373	7-dimethylamino
1374	7-dimethylamino
1375	7-dimethylamino
1376	7-dimethylamino
1377	7-dimethylamino
1378	7-dimethylamino
1379	7-dimethylamino
1380	7-dimethylamino
1381	7-dimethylamino
1382	7-dimethylamino
1383	7-dimethylamino
1384	7-dimethylamino
1385	7-dimethylamino
1386	7-dimethylamino
1387	7-dimethylamino
1388	7-dimethylamino
1389	7-dimethylamino
1390	7-dimethylamino
1391	7-dimethylamino
1392	7-dimethylamino
1393	7-dimethylamino
1394	7-dimethylamino
1395	7-dimethylamino

Compound Number	(R) _m
1396	7-dimethylamino
1397	7-dimethylamino
1398	7-dimethylamino
1399	7-dimethylamino
1400	7-dimethylamino
1401	7-dimethylamino
1402	7-dimethylamino
1403	7-dimethylamino
1404	7-dimethylamino
1405	7-dimethylamino
1406	7-dimethylamino
1407	7-dimethylamino
1408	7-dimethylamino
1409	7-dimethylamino
1410	7-dimethylamino
1411	7-dimethylamino
1412	7-dimethylamino
1413	7-dimethylamino
1414	7-dimethylamino
1415	7-dimethylamino
1416	7-dimethylamino
1417	7-dimethylamino
1418	7-dimethylamino
1419	7-dimethylamino
1420	7-dimethylamino
1421	7-dimethylamino

Compound Number	(R ⁶) _m
1422	7-dimethylamino
1423	7-dimethylamino
1424	7-dimethylamino
1425	7-dimethylamino
1426	7-dimethylamino
1427	7-dimethylamino
1428	7-dimethylamino
1429	7-dimethylamino
1430	7-dimethylamino
1431	7-dimethylamino
1432	7-dimethylamino
1433	7-dimethylamino
1434	7-dimethylamino
1435	7-dimethylamino
1436	7-dimethylamino
1437	7-dimethylamino
1438	7-dimethylamino
1439	7-dimethylamino
1440	7-dimethylamino
1441	7-dimethylamino
1442	7-dimethylamino
1443	7-dimethylamino
1444	7-dimethylamino
1445	7-dimethylamino
1446	7-methoxy; 8-methoxy
1447	7-dimethylamino

Compound Number	(R ⁶) _m
1448	7-dimethylamino
1449	7-dimethylamino
1450	7-dimethylamino
1451	7-dimethylamino

Table 11



[900] The comments below refer to the structures denoted in Table 11 above. According to additional embodiments of the invention, in the above-noted structures IA and IB, R^{1A} and R^{1B} can be independently selected from the group consisting of: ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, iso-propyl, iso-butyl, iso-pentyl, CH₂(C=O)C₂H₅, CH₂OC₂H₅, CH₂CH(OH)C₂H₅, and CH₂O-(4-picoline).

[901] Additionally, R³ and R⁴ can independently be selected from the group consisting of groups (1) – (70) of Table 1 as well as the following: para-methoxy-phenyl, meta-methoxy-phenyl, m-(CH₃)₂N-Ph-, p-(CH₃)₂N-Ph-, I⁻ p-((CH₃)₃-N⁺-Ph-, I⁻ m-((CH₃)₃-N⁺-Ph-, I⁻ p-((CH₃)₃-N⁺-CH₂CH₂-(OCH₂CH₂)₂-O-Ph-, I⁻, p-(N,N-dimethylpiperazine)-(N')-, CH₂-(OCH₂CH₂)₂-O-Ph-, p-CH₃O-Ph-, 3,4,dioxymethylene-Ph, m-CH₃O-, p-F-Ph-, 4-pyridine, N-methyl-4-pyridinium, I⁻, 3-pyridine, N-methyl-3-pyridinium, I⁻, 2-pyridine, p-CH₃O₂C-Ph-, thienyl-2-yl, 5-Cl-thienyl-2-yl, p-F-Ph-, and m-CH₃O-Ph.

[902] Also, R⁶ can be independently selected from the group consisting of: 7-methyl, 7-ethyl, 7-iso-propyl, 7-tert-butyl, 7-OH, 7-OCH₃, 7-O(iso-propyl), 7-SCH₃, 7-SOCH₃,

7-SO₂CH₃, 7-SCH₂CH₃, 7-NH₂, 7-NHOH, 7-NHCH₃, 7-N(CH₃)₂, 7-N⁺(CH₃)₃, I⁻

7-NHC(=O)CH₃, 7-N(CH₂CH₃)₂, 7-NMeCH₂CO₂H, 7-N⁺(Me)₂CH₂CO₂H, I⁻, 7-(N)-morpholine, 7-(N)-azetidine, 7-(N)-N-methylazetidinium, I⁻, 7-(N)-pyrrolidine, 7-(N)-N-methyl-pyrrolidinium, I⁻, 7-(N)-N'-methylpiperazine, 7-(N)-N'-dimethylpiperazinium, I⁻, 7-NH-CBZ, 7-NHC(O)C₅H₁₁, 7-NHC(O)CH₂Br, 7-NH-C(NH)NH₂, 7-(2)-thiophene, 8-methyl, 8-ethyl, 8-iso-propyl, 8-tert-butyl, 8-OH, 8-OCH₃, 8-O(iso-propyl), 8-SCH₃, 8-SOCH₃, 8-SO₂CH₃, 8-SCH₂CH₃, 8-NH₂, 8-NHOH, 8-NHCH₃, 8-N(CH₃)₂, 8-N⁺(CH₃)₃, I⁻, 8-NHC(=O)CH₃, 8-N(CH₂CH₃)₂, 8-NMeCH₂CO₂H, 8-N⁺(Me)₂CH₂CO₂H, I⁻, 8-(N)-morpholine, 8-(N)-azetidine, 8-(N)-N-methylazetidinium, I⁻, 8-(N)-pyrrolidine, 8-(N)-N-methyl-pyrrolidinium, I⁻, 8-(N)-N'-methylpiperazine, 8-(N)-N'-dimethylpiperazinium, I⁻, 8-NH-CBZ, 8-NHC(O)C₅H₁₁, 8-NHC(O)CH₂Br, 8-NH-C(NH)NH₂, 8-(2)-thiophene, 9-methyl, 9-ethyl, 9-iso-propyl, 9-tert-butyl, 9-OH, 9-OCH₃, 9-O(iso-propyl), 9-SCH₃, 9-SOCH₃, 9-SO₂CH₃, 9-SCH₂CH₃, 9-NH₂, 9-NHOH, 9-NHCH₃, 9-N(CH₃)₂, 9-N⁺(CH₃)₃, I⁻, 9-NHC(=O)CH₃, 9-N(CH₂CH₃)₂, 9-NMeCH₂CO₂H, 9-N⁺(Me)₂CH₂CO₂H, I⁻, 9-(N)-morpholine, 9-(N)-azetidine, 9-(N)-N-methylazetidinium, I⁻, 9-(N)-pyrrolidine, 9-(N)-N-methyl-pyrrolidinium, I⁻, 9-(N)-N'-methylpiperazine, 9-(N)-N'-dimethylpiperazinium, I⁻, 9-NH-CBZ, 9-NHC(O)C₅H₁₁, 9-NHC(O)CH₂Br, 9-NH-C(NH)NH₂, and 9-(2)-thiophene.

- [903] Furthermore, R⁶ may also be selected from the group consisting of: 7-(1-aziridine), 7-EtS-, 7-CH₃S(O)-, 7-CH₃S(O)₂-, 7-PhS-, 7CH₃S-, 9-CH₃S-, 7-CH₃O-, 9-CH₃O-, 7-Et-, 7-iPr-, 7-t-Bu-, 7-(1-pyrazole)-, 7-(1-azetidine), 6-CH₃O-, 8-CH₃O-, 9-CH₃-, 7-CH₃, 7-(1-pyrrole), 7-(N)N'-methylpiperazine, 7-CH₃C(=CH₂)-, 7-cyclopropyl, 7-(CH₃)₂NHN-, 7-(N)-azetidine, 7-(N)-pyrrolidine, 7-(CH₃)₂N-, 9-CH₃S-, 7-(CH₃)₂N-, 6-CH₃O-, 7-CH₃O-, 8-CH₃O-, 7-Me-, 9-CH₃, 7-(CH₃)₂N-, 7-cyclopropyl, 8-methyl, 8-ethyl, 8-iso-propyl, 8-tert-butyl, 8-OH, 8-OCH₃, 8-O(iso-propyl), 8-SCH₃, 8-SOCH₃, 8-SO₂CH₃, 8-SCH₂CH₃, 8-NH₂, 8-NHOH, 8-NHCH₃, 8-N(CH₃)₂, 8-N⁺(CH₃)₃, I⁻, 8-NHC(=O)CH₃, 8-N(CH₂CH₃)₂, 8-NMeCH₂CO₂H, 8-N⁺(Me)₂CH₂CO₂H, I⁻, 8-(N)-morpholine, 8-(N)-azetidine, 8-(N)-N-methylazetidinium, I⁻, 8-(N)-pyrrolidine, 8-(N)-N-methyl-pyrrolidinium, I⁻, 8-(N)-N-methyl-morpholinium, I⁻, 8-(N)-N'-methylpiperazine, 8-(N)-N'-dimethylpiperazinium, I⁻, 8-NH-CBZ, 8-NHC(O)C₅H₁₁,

8-NHC(O)CH₂Br, 8-NH-C(NH)NH₂, 8-(2)-thiophene, 9-methyl, 9-ethyl, 9-isopropyl, 9-tert-butyl, 9-OH, 9-OCH₃, 9-O(iso-propyl), 9-SCH₃, 9-SOCH₃, 9-SO₂CH₃, 9-SCH₂CH₃, 9-NH₂, 9-NHOH, 9-NHCH₃, 9-N(CH₃)₂, 9-N⁺(CH₃)₃, I⁻, 9-NHC(=O)CH₃, 9-N(CH₂CH₃)₂, 9-NMeCH₂CO₂H, 9-N⁺(Me)₂CH₂CO₂H, I⁻, 9-(N)-morpholine, 9-(N)-azetidine, 9-(N)-N-methylazetidinium, I⁻, 9-(N)-pyrrolidine, 9-(N)-N-methyl-pyrrolidinium, I⁻, 9-(N)-N-methyl-morpholinium, I⁻, 9-(N)-N'-methylpiperazine, 9-(N)-N'-dimethylpiperazinium, I⁻, 9-NH-CBZ, 9-NHC(O)C₅H₁₁, 9-NHC(O)CH₂Br, 9-NH-C(NH)NH₂, 9-(2)-thiophene, 7-OHC₃, 8-OCH₃, 7-SCH₃, 8-SCH₃, and 6-OCH₃.

- [904] R^{2A} and R^{2B} can be selected from among substituted and unsubstituted C₁ to C₁₀ alkyl wherein the substituent(s) can be selected from among alkylcarbonyl, alkoxy, hydroxy, and nitrogen-containing heterocycles joined to the C₁ to C₁₀ alkyl through an ether linkage. Substituents at the 3-carbon can include ethyl, n-propyl, n-butyl, n-pentyl, isobutyl, isopropyl, -CH₂C(=O)C₂H₅, -CH₂OC₂H₅ and -CH₂O-(4-picoline). Ethyl, n-propyl, n-butyl, and isobutyl are preferred. In certain particularly preferred compounds of the present invention, substituents R^{2A} and R^{2B} are identical, for example n-butyl/n-butyl, so that the compound is achiral at the 3-carbon. Eliminating optical isomerism at the 3-carbon simplifies the selection, synthesis, separation, and quality control of the compound used as an ileal bile acid transport inhibitor. In both compounds having a chiral 3-carbon and those having an achiral 3-carbon, substituents (R⁶) on the benzo ring can include hydrogen, aryl, alkyl, hydroxy, halo, alkoxy, alkylthio, alkylsulfonyl, haloalkyl, haloalkoxy, (N)-hydroxy-carbonylalkyl amine, haloalkylthio, haloalkylsufinyl, haloalkylsufonyl, amino, N-alkylamino, N,N-dialkylamino, (N)-alkoxycarbamoyl, (N)-aryloxycarbamoyl, (N)-aralkyloxycarbamyoyl, trialkylammonium (especially with a halide counterion), (N)-amido, (N)-alkylamido, -N-alkylamido, -N,N-dialkylamido, (N)-haloalkylamido, (N)-sulfonamido, (N)-alkylsulfonamido, (N)-haloalkylsulfonamido, carboxyalkyl-amino, trialkylammonium salt, (N)-carbamic acid, alkyl or benzyl ester, N-acylamine, hydroxylamine, haloalkylamine, carbohydrate, thiophene a trialkyl ammonium salt having a carboxylic acid or hydroxy substituent on one or more of the alkyl substituents, an alkylene bridge having a quaternary ammonium salt substituted thereon, -[O(CH₂)_w]_x-X where x is 2 to 12, w is 2 or 3 and X is a halo or quaternary

ammonium salt, and (N)-nitrogen containing heterocycle wherein the nitrogen of said heterocycle is optional quaternized. Among the preferred species which may constitute R^6 are methyl, ethyl isopropyl, t-butyl, hydroxy, methoxy, ethoxy, isopropoxy, methylthio, iodo, bromo, fluoro, methylsulfinyl, methylsulfonyl, ethylthio, amino, hydroxylamine, N-methylamino, N,N-dimethylamino, N,N-diethylamino, (N)-benzyloxycarbonyl, trimethylammonium, A,-NHC(=O)C₅H₁₁, -NHC(=O)C₆H₁₃, carboxyethylamino, (N)-morpholinyl, (N)-azetidiny, (N)-N-methylazetidinium A, (N)-pyrrolidiny, pyrrolyl, (N)-N-methylpyridinium A, (N)-N-methylmorpholinium A, and N-N'-methylpiperaziny, (N)-bromomethylamido, (N)-N-hexylamino, thiophene, $-N^+(CH_3)_2CO_2H^-$, $-NCH_3CH_2CO_2H$, $-(N)-N'$ -dimethylpiperazinium I⁻, (N)-t-butyloxycarbonyl, (N)-methylsulfonamido, (N)N'-methylpyrrolidinium, and $-(OCH_2CH_2)_3I$, where A is a pharmaceutically acceptable anion. The benzo ring is/can be mono-substituted at the 6, 7 or 8 position, or disubstituted at the 7- and -8 positions. Also included are the 6,7,8-trialkoxy compounds, for example the 6,7,8-trimethoxy compounds. A variety of other substituents can be advantageously present on the 6, 7, 8 and/or 9-positions of the benzo ring, includes, for example, guanidiny, cycloalkyl, carbohydrate (e.g, a 5 or 6 carbon monosaccharide), peptide, and quaternary ammonium salts linked to the ring via poly(oxyalkylene) linkages, e.g., $-(OCH_2CH_2)_x-N^+R^{13}R^{14}R^{15}A$, where x is 2 to 10.

[905] As various changes could be made in the above methods and apparatus without departing from the scope of the invention, it is intended that all matter contained in the above description be interpreted as illustrative and not in a limiting sense. All documents mentioned in this application are expressly incorporated by reference as if fully set forth at length.

[906] All patents, publication or other references mentioned in this application are incorporated herein by reference in their entirety. When introducing elements of the present invention or the preferred embodiment(s) thereof, the articles "a", "an", "the" and "said" are intended to mean that there are one or more of the elements. The terms "comprising", "including" and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements.